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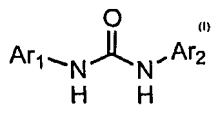
(54) Title: DIARYL UREAS AS CB1 ANTAGONISTS



(57) Abstract: Compounds of Formula I are provided. In which the variables are as described herein. Such compounds may be used to modulate CB1 activity in vivo or in vitro, and are particularly useful in the treatment of conditions responsive to CB1 modulation in humans, domesticated companion animals and livestock animals, including appetite disorders, obesity and addictive disorders. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies and various in vitro assays.

DIARYL UREAS AS CB1 ANTAGONISTS

FIELD OF THE INVENTION

This invention relates generally to diaryl ureas, and to the use of such compounds to treat conditions responsive to cannabinoid receptor-1 (CB1) modulation. The invention further relates to the use of such compounds as reagents for the identification of other agents that bind to CB1, and as probes for the detection and localization of CB1.

BACKGROUND OF THE INVENTION

Obesity is the most common nutritional problem in developed countries. This condition is often both harmful and costly, as it increases the likelihood of developing serious health conditions (such as cardiovascular diseases and diabetes) and complicates numerous chronic conditions such as respiratory diseases, osteoarthritis, osteoporosis, gall bladder disease and dyslipidemias. Fortunately, however, many of the conditions caused or exacerbated by obesity can be resolved or dramatically improved by weight loss.

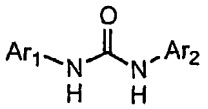
Once considered merely a behavioral problem (*i.e.*, the result of voluntary hyperphagia), obesity is now recognized as a complex multifactorial disease involving defective regulation of food intake, food-induced energy expenditure and the balance between lipid and lean body anabolism. Both environmental and genetic factors play a role in the development of obesity. As a result, treatment programs that focus entirely on behavior modification have limited efficacy and are associated with recidivism rates exceeding 95%. Pharmacotherapy is now seen as a critical component of weight loss and subsequent weight management.

Currently available prescription drugs for managing obesity generally reduce weight by inducing satiety or decreasing dietary fat absorption. Such drugs, however, often have unacceptable side effects. Several, such as the older adrenergic weight-loss drugs (*e.g.*, amphetamine, methamphetamine, and phenmetrazine), which act via dopamine pathways, are no longer recommended because of the risk of their abuse. Fenfluramine and dexfenfluramine, both serotonergic agents used to regulate appetite, are also no longer available for use.

Thus, there exists a need for more effective agents for promoting weight loss and for reducing or preventing weight gain. In addition, there exists an unmet need for more effective agents for the treatment of alcohol and tobacco dependence. The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides diaryl ureas as CB1 antagonists. Such compounds generally satisfy Formula I:


Formula I

or are a pharmaceutically acceptable salt of such a compound.

Within Formula I:

Ar_1 and Ar_2 are independently chosen from phenyl, naphthyl and 5- to 10-membered heteroaryl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 4 substituents that are independently chosen from R_x; in certain embodiments, Ar_1 and Ar_2 are independently chosen from phenyl and 5- or 6-membered heteroaryl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(a) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(b) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

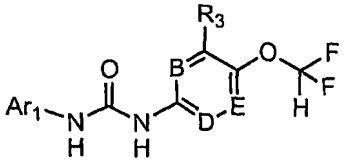
M is absent, O, C(=O) (*i.e.*,), OC(=O) (*i.e.*,), C(=O)O(*i.e.*,), O-C(=O)O (*i.e.*,), $S(O)_m$ (*i.e.*, -S-,  or), $N(R_z)$ (*i.e.*, ), C(=O)$N(R_z)$ (*i.e.*, ), C(=NH)$N(R_z)$ (*i.e.*,), $N(R_z)$C(=O) (*i.e.*,), $N(R_z)$C(=NH) (*i.e.*,), $N(R_z)$C(=O)O (*i.e.*, ), OC(=O)$N(R_z)$ (*i.e.*,), $N(R_z)S(O)_m$ (*e.g.*,), $S(O)_mN(R_z)$ (*e.g.*,) or $N[S(O)_mR_z]S(O)_m$ (*e.g.*, ); wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(c) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is optionally substituted, and is preferably substituted

with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl.

Within certain aspects, diaryl ureas of Formula I further satisfy Formula II:



Formula II

or are a pharmaceutically acceptable salt of such a compound.

Within Formula II:

B, D and E are independently CH or N;

R_3 is hydrogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

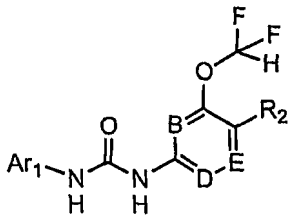
Ar_1 is as described above; in certain embodiments, Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents that are independently chosen from R_x; such that if R_3 is hydrogen, then Ar_1 is substituted with at least one substituent that is not a halogen; and

Each R_x is independently:

(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is optionally substituted, and each of which is preferably substituted with from 0 to 3 substituents independently chosen from hydroxy, amino, cyano, C_1-C_4alkyl and C_1-C_4alkoxy.

Within further aspects, diaryl ureas of Formula I further satisfy Formula III:



Formula III

or are a pharmaceutically acceptable salt of such a compound.

Within Formula III:

B, D and E are independently CH or N;

R_2 is hydrogen, halogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

Ar_1 is as described above; in certain embodiments, Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is optionally substituted, and each of which is preferably substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is optionally substituted, and each of which is preferably substituted with from 0 to 3 substituents independently chosen from hydroxy, amino and cyano.

In certain aspects, compounds as described above are non-competitive CB1 antagonists.

Diaryl ureas provided herein are CB1 antagonists. In certain aspects, such diaryl ureas exhibit a K_i of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in a CB1 ligand binding assay and/or have an EC_{50} or IC_{50} value of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in an assay for determination of CB1 agonist or antagonist activity.

In certain embodiments, diaryl urea CB1 antagonists provided herein exhibit no detectable agonist activity.

Within certain aspects, diaryl ureas as described herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one diaryl urea as described herein in combination with a physiologically acceptable carrier or excipient.

The present invention further provides pharmaceutical compositions, comprising (a) a first agent that is a diaryl urea as described above, (b) a second agent that is suitable for treating an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss; and (c) a physiologically acceptable carrier or excipient.

The present invention also provides packaged pharmaceutical preparations, comprising: (a) a composition comprising a diaryl urea as described herein in a container; and (b) instructions for using the composition to treat one or more conditions responsive to CB1 modulation.

The present invention further provides methods for treating a condition responsive to CB1 modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one diaryl urea as described herein. Such conditions include, for example, appetite disorders, obesity, dependency disorders such as alcohol dependency and nicotine dependency, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, memory disorders, cognitive disorders, movement disorders and bone loss.

In further aspects, methods are provided for suppressing appetite in a patient, comprising administering to the patient an appetite reducing amount of at least one diaryl urea as described herein.

Methods are further provided herein for identifying a non-competitive CB1 antagonist, comprising: (a) contacting CB1 with (i) a labeled diaryl urea as described above that is a non-competitive CB1 antagonist and (ii) a test compound, under conditions that permit binding of the labeled diaryl urea to CB1; (b) removing unbound labeled diaryl urea and unbound test compound; (c) detecting a signal that corresponds to the amount of labeled diaryl urea bound to CB1; and (d) comparing the signal to a reference signal that corresponds to the amount of labeled diaryl urea bound to CB1 in the absence of test compound.

Within further aspects, the present invention provides methods for determining the presence or absence of CB1 in a sample, comprising: (a) contacting a sample with a diaryl urea as described herein under conditions that permit binding of the diaryl urea to CB1; and (b) detecting a signal indicative of a level of the diaryl urea bound to CB1.

In yet another aspect, the invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

As noted above, the present invention provides diaryl urea CB1 antagonists. Such compounds may be used *in vitro* or *in vivo* in a variety of contexts as described herein.

TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. If a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, R_x, Ar_1). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "diaryl urea" encompasses all compounds of Formula I, and includes pharmaceutically acceptable salts of such compounds.

A "pharmaceutically acceptable salt" of a compound is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically

acceptable salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each diaryl urea may, but need not, be formulated as a hydrate, solvate or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided herein are prodrugs of the diaryl ureas described herein. A "prodrug" is a compound that may not fully satisfy the structural requirements of Formula I, but is modified *in vivo*, following administration to a patient, to produce a diaryl urea of Formula I. For example, a prodrug may be an acylated derivative of a diaryl urea. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C_1-C_8alkyl), from 1 to 6 carbon atoms (C_1-C_6alkyl) and from 1 to 4 carbon atoms (C_1-C_4alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl or 3-methylpentyl. "C_0-C_4alkyl" refers to a single covalent bond (C_0) or an alkyl group having 1, 2, 3 or 4 carbon atoms; "C_0-C_6alkyl" refers to a single covalent bond or a C_1-C_6alkyl group; "C_0-C_8alkyl" refers to a single covalent bond or a C_1-C_8alkyl group.

"Alkylene" refers to a divalent alkyl group, as defined above. C_0-C_4alkylene is a single covalent bond or an alkylene group having 1, 2, 3 or 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include C_2-C_8alkenyl, C_2-C_6alkenyl and C_2-C_4alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C_2-C_8alkynyl, C_2-C_6alkynyl and C_2-C_4alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a saturated or partially saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl or a partially saturated variant thereof. Certain cycloalkyl groups are C_3-C_8cycloalkyl, in which the ring contains from 3 to 8 ring members, all of which are carbon. A "(C_3-C_8cycloalkyl)C_0-C_4alkyl" is a C_3-C_8cycloalkyl group linked via a single covalent bond or a C_1-C_4alkylene group.

By "alkoxy," as used herein, is meant an alkyl group as described above attached via an oxygen bridge. Alkoxy groups include C_1-C_6alkoxy and C_1-C_4alkoxy groups, which have from 1 to 6 or 1 to 4 carbon atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are representative alkoxy groups.

"Alkylthio" refers to an alkyl group as described above attached via a sulfur bridge.

"Alkylsulfonyl" refers to groups of the formula –(SO_2)–alkyl, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include C_1-C_6alkylsulfonyl and C_1-C_4alkylsulfonyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

The term "alkanoyl" refers to an acyl group (*e.g.*, –(C=O)–alkyl), where attachment is through the carbon of the keto group. Alkanoyl groups include C_2-C_8alkanoyl, C_2-C_6alkanoyl and C_2-C_4alkanoyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. "C_1alkanoyl" refers to –(C=O)H, which (along with C_2-C_8alkanoyl) is encompassed by the term "C_1-C_8alkanoyl." Ethanoyl is C_2alkanoyl.

An "alkanone" is a ketone group in which carbon atoms are in a linear or branched alkyl arrangement. "C_3-C_8alkanone," "C_3-C_6alkanone" and "C_3-C_4alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. A C_3 alkanone has the structure –CH_2–(C=O)–CH_3.

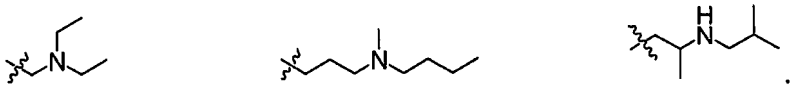
Similarly, "alkyl ether" refers to a linear or branched ether substituent. Alkyl ether groups include C_2-C_8alkyl ether, C_2-C_6alkyl ether and C_2-C_4alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. A C_2 alkyl ether has the structure –CH_2–O–CH_3.

The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*i.e.*, a group having the general structure –C(=O)–O–alkyl). Alkoxycarbonyl groups include C_1-C_8, C_1-C_6 and C_1-C_4alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkyl portion of the group. "C_1alkoxycarbonyl" refers to –C(=O)–O–CH_3.

"Alkanoyloxy," as used herein, refers to an alkanoyl group linked via an oxygen bridge (*i.e.*, a group having the general structure –O–C(=O)–alkyl). Alkanoyloxy groups include C_2-C_8, C_2-C_6 and C_2-C_4alkanoyloxy groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively. "C_2alkanoyloxy" refers to –O–C(=O)–CH_3.

"Alkylamino" refers to a secondary or tertiary amine having the general structure –NH–alkyl or –N(alkyl)(alkyl), wherein each alkyl may be the same or different. Such groups include, for example, mono- and di-(C_1-C_8alkyl)amino groups, in which each C_1-C_8alkyl may be the same or different, as well as mono- and di-(C_1-C_6alkyl)amino groups and mono- and di-(C_1-C_4alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene group (*i.e.*, a group having the general structure –alkyl–NH–alkyl or –alkyl–N(alkyl)(alkyl)) in which each alkyl is selected independently. Such groups include, for example, mono- and di-(C_1-C_8alkyl)aminoC_1-C_8alkyl, mono- and di-(C_1-C_6alkyl)aminoC_1-C_6alkyl and mono- and di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, in which each alkyl may be the same or different. "Mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl" refers to a mono- or di-(C_1-C_6alkyl)amino group linked via a single covalent bond or a C_1-C_4alkylene group. The following are representative alkylaminoalkyl groups:



The term "aminocarbonyl" refers to an amide group (*i.e.*, -C(=O)NH_2).

The term "aminosulfonyl" refers to a sulfonamide group (*i.e.*, -SO_2NH_2).

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" is an alkyl group that is substituted with one or more independently chosen halogens (*e.g.*, "C_1-C_8haloalkyl" groups have from 1 to 8 carbon atoms; "C_1-C_6haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "C_1-C_8haloalkoxy" groups have 1 to 8 carbon atoms.

A dash ("-") that is not between two letters or numbers is used to indicate a point of attachment for a substituent. For example, -C(=O)NH_2 is attached through the carbon atom.

A "carbocycle" has from 1 to 3 fused, pendant or spiro rings, each of which has only carbon ring members. Typically, a carbocycle that has a single ring contains from 3 to 8 ring members (*i.e.*, C_3-C_8carbocycles); rings having from 4 or 5 to 7 ring members (*i.e.*, C_4-C_7carbocycles or C_5-C_7carbocycles) are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Carbocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a carbocycle may be a cycloalkyl

group (*i.e.*, each ring is saturated or partially saturated as described above) or an aryl group (*i.e.*, at least one ring within the group is aromatic). Representative aromatic carbocycles are phenyl, naphthyl and biphenyl. In certain embodiments preferred carbocycles have a single ring, such as phenyl and C_3-C_8cycloalkyl groups.

A "heterocycle" (also referred to herein as a "heterocyclic group") has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom independently chosen from oxygen, sulfur and nitrogen, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO_2. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Certain heterocycles are heteroaryl groups (*i.e.*, at least one heterocyclic ring within the group is aromatic), such as a 5- to 10-membered heteroaryl (which may be monocyclic or bicyclic) or a 6-membered heteroaryl (*e.g.*, pyridyl or pyrimidyl). Other heterocycles are heterocycloalkyl groups (*i.e.*, no ring is aromatic).

A "substituent," as used herein, refers to a molecular moiety other than hydrogen that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (such as a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described herein, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound *(i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents).

"CB1," as used herein, refers to the human cannabinoid receptor reported by Hoeche et al. (1991) *New Biol. 3(9)*:880-85, as well as allelic variants thereof and homologues thereof found in other species.

A "CB1 antagonist" is a compound that detectably inhibits signal transduction mediated by CB1. Such inhibition may be determined using the representative agonist-induced GTP binding

assay provided in Example 8. Preferred CB1 antagonists have an IC_{50} of 2 μM or less in this assay, more preferably 1 μM or less, and still more preferably 500 nM or less or 100 nM or less. In certain embodiments, the CB1 antagonist is specific for CB1 (*i.e.*, the IC_{50} value in a similar assay performed using the predominantly peripheral cannabinoid receptor CB2 is greater than 2 μM and/or the IC_{50} ratio (CB2/CB1) is at least 10, preferably 100, and more preferably at least 1000). CB1 antagonists preferably have minimal agonist activity (*i.e.*, induce an increase in the basal activity of CB1 that is less than 5% of the increase that would be induced by one EC_{50} of the agonist CP55,940, and more preferably have no detectable agonist activity within the assay described in Example 8). CB1 antagonists for use as described herein are generally non-toxic. CB1 antagonists include neutral antagonists and inverse agonists.

A "neutral antagonist" of CB1 is a compound that inhibits the activity of CB1 agonist (*e.g.*, endocannabinoids) at CB1, but does not significantly change the basal activity of the receptor (*i.e.*, within a GTP binding assay as described in Example 8 performed in the absence of agonist, CB1 activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists may, but need not, also inhibit the binding of agonist to CB1.

An "inverse agonist" of CB1 is a compound that reduces the activity of CB1 below its basal activity level in the absence of activating concentrations of agonist. Inverse agonists may also inhibit the activity of agonist at CB1, and/or may inhibit binding of CB1 agonist to CB1. The ability of a compound to inhibit the binding of CB1 agonists to the CB1 receptor may be measured by a binding assay, such as the radioligand binding assay given in Example 7. The reduction in basal activity of CB1 produced by an inverse agonist may be determined from a GTP binding assay, such as the assay of Example 8.

A "non-competitive CB1 antagonist" is a CB1 antagonist that (1) does not detectably inhibit binding of CB1 agonist (*e.g.*, CP55,940) to CB1 at antagonist concentrations up to 10 μM (*e.g.*, may have no effect on binding of agonist or may enhance agonist binding) and (2) reduces the maximal functional response elicited by agonist. Compounds that satisfy these two conditions may be identified using the assays provided herein. Such compounds generally do not display detectable activity in the competition binding assay described in Example 7. In functional assays, a non-competitive antagonist concentration-dependently reduces the maximal functional response elicited by agonist without altering agonist EC_{50}. The suppression of functional activity by a non-competitive antagonist cannot be overcome by increasing agonist concentrations (*i.e.*, the antagonist activity is insurmountable).

A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (*e.g.*, provides detectable relief from a condition being treated). Such relief may be detected using any appropriate criteria, including the alleviation of one or more symptoms of dependency or an appetite disorder, or the promotion of weight loss. In the

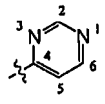
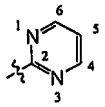
case of appetite suppression, a therapeutically effective amount is sufficient to decrease patient appetite, as assessed using patient reporting or actual food intake. Such an amount is referred to herein as an "appetite reducing amount." A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to result in detectable alteration in CB1-mediated signal transduction (using an assay provided herein). The discernible patient benefit may be apparent after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a predetermined regimen, depending upon the indication for which the compound is administered.

A "patient" is any individual treated with a compound as provided herein. Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to CB1 modulation or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic in a patient considered to be at risk for the development of such symptoms).

DIARYL UREA CB1 ANTAGONISTS

As noted above, the present invention provides diaryl ureas that may be used in a variety of contexts, including in the treatment of appetite disorders, obesity and addictive disorders. Such compounds may also be used within *in vitro* assays (*e.g.*, assays for CB1 activity), as probes for detection and localization of CB1 and within assays to identify other CB1 antagonists, including non-competitive CB1 antagonists.

Diaryl ureas provided herein satisfy Formula I, and may further satisfy one or more additional formulas provided herein (*e.g.*, Formula II or Formula III).

Within certain diaryl ureas, Ar_1 and Ar_2 are independently phenyl, pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently located *meta* or *para* to the point of attachment. In other words, if Ar_1 and Ar_2 are both phenyl, then each of Ar_1 and Ar_2 is independently unsubstituted or substituted at the 3, 4 and/or 5 position. Similarly, if Ar_1 or Ar_2 is pyridine-2-yl, the pyridine-2-yl is either unsubstituted or substituted at the 4, 5 and/or 6 position. The pyrimidine group  is preferably substituted at the 2 and/or 6 position, and  is preferably substituted at the 4, 5 and/or 6 position. Preferably, each substituent is independently:

(a) halogen, hydroxy or cyano; or

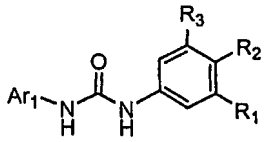
(b) C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_4alkanoyl, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl or a 5- or 6-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl and C_1-C_4haloalkyl.

Within other diaryl ureas, at least one of Ar_1 and Ar_2 is a 9- or 10-membered heteroaryl, such as quinolinyl, quinazolinyl, benzoxazolyl, benzimidazolyl, indazolyl or benzofuranyl, each of which is optionally substituted as described above.

Ar_1, within certain such compounds, is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment (*i.e.*, Ar_1 is not *ortho*-substituted), and each of which is independently C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy. Representative such Ar_1 groups include, for example, phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl and 4-(C_1-C_4alkoxy)-phenyl.

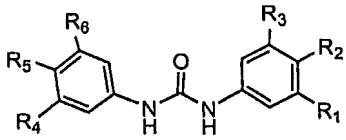
Ar_2, within certain such compounds, is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle. For example, Ar_2 may be phenyl that is substituted with exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy. In other such compounds, Ar_2 is phenyl that is substituted with exactly one substituent chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy. Representative such Ar_2 groups include, for example, phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-cyano-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-cyano-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl, 4-(C_1-C_4alkoxy)-phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl and 4-acetyl-phenyl.

Certain compounds of Formula I further satisfy Formula Ia:



Formula Ia

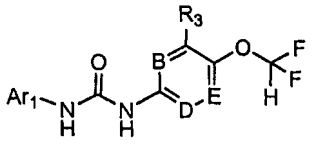
wherein R_1, R_2 and R_3 are independently chosen from hydrogen and R_x, and wherein at least one of R_1 and R_2 is not hydrogen. Within certain such compounds, R_1, R_2 and R_3 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl and 5- and 6-membered heterocycles. Still further compounds of Formula I or Ia further satisfy Formula Ib:



Formula Ib

wherein R_4, R_5 and R_6 are independently chosen from hydrogen and R_x, and wherein at least one of R_4 and R_5 is not hydrogen. Within certain such compounds, R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

Certain compounds of Formula I further satisfy Formula II:



Formula II

wherein:

B, D and E are independently CH or N (in certain embodiments, B, D and E are each CH);

R_3 is hydrogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; such that if R_3 is hydrogen, then Ar_1 is substituted with at least one substituent that is not a halogen; and

Each R_x is independently:

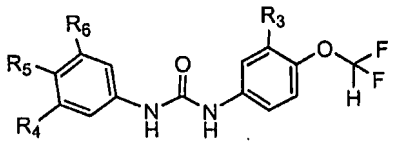
(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, amino, cyano, C_1-C_4alkyl and C_1-C_4alkoxy.

Within certain such compounds, R_3 is hydrogen, methoxy or difluoromethoxy. Ar_1, within certain such compounds, is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle. Representative such Ar_1 groups include, for example, phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl, 4-(C_1-C_4alkoxy)-phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl and 4-acetyl-phenyl. In certain embodiments, Ar_1 is phenyl that is substituted with exactly one or exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

As noted above, if R_3 is hydrogen, then Ar_1 is substituted with at least one substituent that is not a halogen. In other words, Ar_1 in such compounds is not unsubstituted or substituted with one or more halogens unless an additional non-halogen substituent is also present as a substituent of Ar_1.

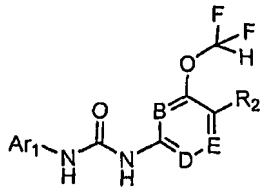
Certain compounds of Formula II further satisfy Formula IIa:



Formula IIa

wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

Certain compounds of Formula I further satisfy Formula III:



Formula III

wherein:

B, D and E are independently CH or N (in certain embodiments, B, D and E are each CH);

R_2 is hydrogen, halogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

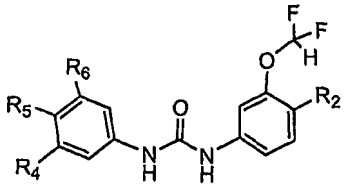
Each R_x is independently:

(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, amino and cyano.

Within certain such compounds, R_2 is hydrogen, halogen, methoxy or difluoromethoxy. Ar_1, within certain such compounds, is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle. For example, Ar_1 may be phenyl that is substituted with exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy. Alternatively, Ar_1 is phenyl that is substituted with exactly one substituent chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy. Representative such Ar_1 groups include, for example, phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl, 4-(C_1-C_4alkoxy)-phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl and 4-acetyl-phenyl.

Certain compounds of Formula III further satisfy Formula IIIa:



Formula IIIa

wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

Representative compounds provided herein include, but are not limited to, those specifically described in the Examples below. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt.

As noted above, compounds provided herein are CB1 antagonists. Certain such compounds are non-competitive CB1 antagonists. In addition, or alternatively, certain compounds provided herein display CB1 specificity. CB1 antagonist activity may be confirmed using an agonist-induced GTP binding assay, such as the assay described in Example 8. Such assays employ a CB1-containing cell membrane preparation (*e.g.*, a preparation of membranes of insect cells that recombinantly express CB1) to determine the effect of a test compound on CB1 agonist-induced GTP binding to CB1. Briefly, a first cell membrane preparation comprising CB1 is contacted with: (i) labeled GTP; (ii) a CB1 agonist; and (iii) a test compound to yield a test membrane preparation. Simultaneously, or in either order, a second cell membrane preparation comprising CB1 is contacted with: (i) labeled GTP; and (ii) a CB1 agonist to yield a control membrane preparation. The labeled GTP is preferably GTPγ^{35}S; a representative CB1 agonist is CP55,940. Such contact is performed under conditions that are suitable for GTP binding to CB1, such as the conditions described in Example 8. The concentrations of labeled GTP and CB1 agonist used are generally concentrations that are sufficient to result in a detectable increase in the amount of labeled GTP bound to the membrane preparation in the presence of CB1 agonist. Such concentrations may be determined by routine experimentation; representative suitable concentrations are provided in Example 8. Generally, a range of test compound concentrations is used (*e.g.*, ranging from 10^{-10}M to 10^{-5}M).

After sufficient contact (*e.g.*, incubation) to allow GTP binding to the membrane preparations, a signal that corresponds to (represents) the amount of bound, labeled GTP is detected (typically, unbound labeled GTP is first removed via a washing step). In other words, simultaneously or in either order: (i) a test signal that represents an amount of bound, labeled GTP in the test membrane preparation is detected; and (ii) a control signal that represents an amount of bound, labeled GTP in the control membrane preparation is detected. The nature of the signal detected is determined by the type of label used. For example, if the GTP is radioactively labeled, the signal detected is radioactive decay (*e.g.*, via liquid scintillation spectrometry). The CB1 antagonist activity of the test compound is then determined by comparing the test signal with the control signal. A test signal that is lower than the control signal indicates that the test compound is a CB1 antagonist.

In certain embodiments, preferred compounds are cannabinoid receptor-specific. This means that they only bind to, activate, or inhibit the activity of certain receptors other than cannabinoid receptors (preferably other than CB1) with affinity constants of greater than 100 nanomolar, preferably greater than 1 micromolar, more preferably greater than 4 micromolar.

Alternatively, or in addition, such compounds exhibit 200-fold greater affinity for CB1 than for other non-cannabinoid cellular receptors. Such other non-cannabinoid cellular receptors include histamine receptors, bioactive peptide receptors (including NPY receptors such as NPY Y5), and hormone receptors (*e.g.*, melanin-concentrating hormone receptors). Assays for evaluating binding to such receptors are well known, and include those disclosed in US patent 6,566,367, which is incorporated herein by reference for its disclosure of NPY receptor binding assays in Example 676 columns 82-83; and in PCT International Application Publication No. WO 02/094799 which is incorporated herein by reference for its disclosure of an MCH receptor binding assay in Example 2, pages 108-109.

The usefulness of the compounds provided herein for the various diseases and disorders may be demonstrated in animal disease models that are known in the art, such as (but not limited to):

Colombo et al. (1998) *Life Sciences 63*:113-17 and Vickers and Kennett (2005) *Curr. Drug. Targets 6*:215-23 –food intake and weight loss (rats)

Simiand et al. (1998) *Behavioral Pharm. 9*:179-181 – sweet food intake (marmosets)

Rowland et al. (2001) *Psychopharm. 159*:111-16 – food intake (rats)

Arnone et al. (1997) *Psychopharm. 132*:104-106 – sucrose and ethanol intake (mice)

Colombo et al. (2004) *Eur. J. Pharmacol. 498*:119-23 – alcohol motivational properties (rats)

Serra et al. (2002) *Eur. J. Pharmacol. 443*:95-97 – alcohol deprivation effect (rats)

Rubino et al. (2000) *Life Sciences 22*:2213-29 – opiate withdrawal syndrome (rats)

Chaperon et al. (1998) *Psychopharm. 135*:324-32 – motor activity, place conditioning (rats)

Abraham et al. (1993) *J. Clin. Invest. 93*:776 and Milne and Piper (1995) *Eur. J. Pharmacol. 282*:243 – bronchial hyperresponsiveness (sheep and guinea pigs)

Kadoi et al. (2005) *British Journal of Anaesthesia 94(5)*:563-68 – septic shock (rats)

Batkai et al. (2001) *Nature Medicine 7(7)*:827-32 –vasodilation in liver cirrhosis (rats)

Tsusumi et al. (2000) *Biol. Pharm. Bull. (Japan) 23(5)*:657-59 – constipation (monkeys)

Kapur (2001) *J. Pathology 194(3)*:277-88 – chronic intestinal pseudo-obstruction (rodents)

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable.

Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described herein.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 10, herein. In other words, cells treated as described in Example 10 with 100 μM of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p<0.1$ level or more preferably at the $p<0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than

50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05. 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC_{50} or IC_{50} for the compound.

In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC_{50} or IC_{50} for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC_{50} or IC_{50} for the compound. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. For example, such compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF DIARYL UREA CB1 ANTAGONISTS

Diaryl ureas provided herein may generally be prepared using standard synthetic methods. In general, starting materials are commercially available from suppliers such as Sigma-Aldrich

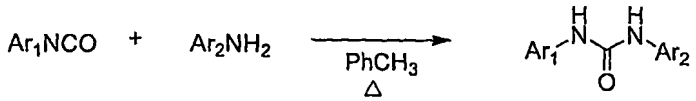
Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon appreciated by those skilled in the art. It will be apparent that the reagents and synthetic transformations in the following Schemes can be readily modified to produce additional diaryl ureas. Each variable in the following Schemes refers to any group consistent with the description of the compounds provided herein.

When a protecting group is required, an optional deprotection step may be employed. Suitable protecting groups and methodology for protection and deprotection, such as those described in *Protecting Groups in Organic Synthesis* by T. Greene, are well known. Compounds and intermediates requiring protection/deprotection will be readily apparent.

Certain definitions used in the following Schemes and in the Examples include:

$CDCl_3$	deuterated chloroform
DIEA	diisopropylethylamine
DPPA	diphenylphosporyl azide
EtOAc	ethyl acetate
h	hour(s)
^1H NMR	proton nuclear magnetic resonance
Hz	hertz
LC/MS	liquid chromatography/mass spectrometry
MHz	megahertz
min	minute(s)
MS	mass spectrometry
(M+1)	mass + 1
δ	chemical shift
Ph	phenyl
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine) palladium (0)

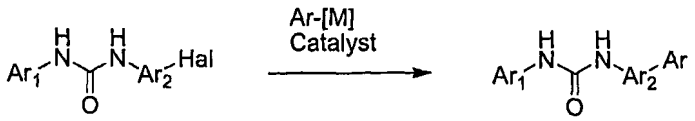
Scheme 1. Preparation of compounds of Formula I



Scheme 1 illustrates a method for preparing diaryl ureas from readily available aminoaryl compounds and arylisocyanates. In this method, on equivalent of arylisocyanate is heated an aminoaryl derivative in an appropriate solvent. Commonly used solvents for the reaction include but are not limited to toluene, tetrahydrofuran and dioxane. Those skilled in the art will recognize

that the choice of solvent and reaction temperature may be modified to optimize the reaction for various reactant combinations.

Scheme 2. Preparation of compounds of Formula I wherein R_2 is aryl or heteroaryl



Hal = Br, Cl, I

Scheme 2 illustrates a method for preparing diaryl ureas wherein Ar_2 is substituted with an aryl or heteraryl group (Ar). Although illustrated for substitution on Ar_2, the same methodology may be applied to incorporate aryl and heteraryl substituents at all positions allowed for R_x in Formula I. In Scheme 2, the haloaryl urea is coupled to various aryl groups via a transition metal-catalyzed coupling reaction with a metalloaryl reagent (Ar-[M]). Suitable reagent/catalyst pairs include aryl boronic acid/palladium(0) (Suzuki reaction; N. Miyaura and A. Suzuki, Chemical Review 1995, 95, 2457) and aryl trialkylstannane/palladium(0) (Stille reaction; T. N. Mitchell, Synthesis 1992, 803). Palladium(0) represents a catalytic system made of a various combination of metal/ligand pair which includes, but not limited to, tetrakis(triphenylphosphine)palladium(0), palladium(II) acetate/tri(o-tolyl)phosphine, tris(dibenzylideneacetone)dipalladium(0)/tri-tert-butylphosphine and dichloro[1,1'-bis(diphenylphosphine)ferrocene]palladium(0). Nickel(II) represents a nickel-containing catalyst such as [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II).

In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ^{14}C), hydrogen (*e.g.*, ^{3}H), sulfur (*e.g.*, ^{35}S) or iodine (*e.g.*, ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently

performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more compounds provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, syrups or elixirs. Within other embodiments, pharmaceutical compositions may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with suitable excipients, such as suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum

acacia); and dispersing or wetting agents *(e.g.,* naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and/or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.,* arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.,* olive oil or arachis oil), a mineral oil (*e.g.,* liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.,* gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.,* soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.,* sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.,* polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (*e.g.,* ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.,* butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.,* lanolin); mixtures of water and

organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound(s) provided herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be formulated as suppositories (*e.g.*, for urethral or rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols. Suppositories include those described by, for example, U.S. Patent No. 6,846,823, which is hereby incorporated by reference for its teaching of the preparation and administration of pharmaceutical compositions for urethral or rectal administration.

Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (*e.g.*, dichlorodifluoromethane or trichlorofluoromethane).

Pharmaceutical compositions may be formulated as controlled release formulations (*i.e.*, a formulation such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration), which may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a rate that blood (*e.g.*, plasma) concentrations are maintained within the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours.

Controlled release may be achieved by combining the active ingredient(s) with a matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e) providing one or more passageways through the coating. The amount of modulator contained within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed. Active ingredient(s) may be combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is

smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free. Coatings that regulate release of the modulator include pH-independent coatings, pH-dependent coatings (which may be used to release modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition or one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, diputyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels or to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose),

cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed my methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.*, US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 5,524,060; 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Compounds are generally administered in a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage units will generally contain from about 10 μg to about 500 mg of an active ingredient. In certain embodiments, the dosage unit contains an amount of the compound that is sufficient to effect a decrease in the patient's caloric intake (*i.e.*, an appetite-suppressing amount) following single dose administration or repeated administration according to a predetermined regimen. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions may be used for treating a condition responsive to CB1 modulation. Such conditions include, for example:

appetite disorders (*e.g.*, binge eating disorder, bulimia, anorexia);

obesity and complications associated therewith, including left ventricular hypertrophy);

weight loss or control (*e.g.*, reducing calorie or food intake and/or appetite suppression);
addictive disorders such as:

alcohol dependency (*e.g.*, alcohol abuse, addiction and/or dependency including treatment for abstinence, craving reduction and relapse prevention of alcohol intake);

nicotine dependency (*e.g.*, smoking addiction, cessation and/or dependency including treatment for craving reduction and relapse prevention of tobacco smoking); and

drug dependency (*e.g.*, chronic treatment with or abuse of drugs such as opioids, barbiturates, cannabis, cocaine, amphetamines, phencyclide, hallucinogens, and/or benzodiazepines); and

bone loss (*e.g.*, resulting from estrogen deficiency).

Other conditions responsive to CB1 modulation include CNS disorders (*e.g.*, anxiety, depression, panic disorder, bipolar disorder, psychosis, schizophrenia, behavioral addiction, dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), attention deficit disorder (ADD/ADHD), stress, amnesia, cognitive disorders, memory disorders, neurodegeneration, cerebellar and spinocerebellar disorder, cranial trauma, cerebral vascular accidents, obsessive-compulsive disorder, senile dementia, impulsivity), thymic disorders, septic shock, Tourette's syndrome, Huntington's chorea, Raynaud's syndrome, peripheral neuropathy, diabetes (type II or non insulin dependent), glaucoma, migraine, seizure disorders, epilepsy, locomotor disorders (movement disorders induced by medicaments, dyskinesias or Parkinson's disease), respiratory disorders (such as asthma), gastrointestinal disorders (*e.g.*, dysfunction of gastrointestinal motility or intestinal propulsion, constipation, chronic intestinal pseudo-obstruction, irritable bowel syndrome, Crohn's disease), liver cirrhosis, vomiting, diarrhea, ulcer, multiple sclerosis, cardiovascular disorder, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, a disorder of the endocrine system, urinary or bladder disorders, cancer, infectious disease, inflammation, infection, cancer, neuroinflammation (such as atherosclerosis), Guillain-Barre syndrome, viral encephalitis, cranial trauma, sepsis or a reproductive disorder. In certain embodiments, the condition responsive to CB1 modulation is an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder and/or bone loss.

Certain pharmaceutical compositions provided herein comprise a first agent that is a diaryl urea of Formula I in combination with a second agent that differs in structure from the first agent and is suitable for treating the condition of interest. In certain embodiments, the second agent is not a diaryl urea of Formula I; in further embodiments, the second agent is not a CB1 antagonist. In certain such compositions, the second agent is suitable for treating an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder and/or

bone loss. Representative second agents for use within such pharmaceutical compositions include anti-obesity agents such as MCH receptor antagonists, apo-B/MTP inhibitors, 11β-hydroxy steroid dehydrogenase-1 inhibitors, peptide YY_3-36 or an analog thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogues, 5-HT2c receptor agonists, leptin or an analog thereof, leptin receptor agonists, galanin antagonists, lipase inhibitors, bombesin agonists, neuropeptide-Y receptor antagonists, thyromimetic agents, dehydroepiandrosterone or analog thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists, and neuromedin U receptor agonists. Such agents include, for example, phentermine, orlistat and sibutramine (*e.g.*, sibutramine HCl monohydrate, sold as Meridia® (Abbott Laboratories)).

Certain second agents for use in weight management are MCH receptor antagonists. Preferably, such MCH receptor antagonists detectably inhibit MCH binding to MCHR1 and/or MCHR2 (as determined using a standard *in vitro* MCH receptor ligand binding assay and/or calcium mobilization assay) at submicromolar concentrations, preferably at nanomolar concentrations, and more preferably at subnanomolar concentrations. In certain preferred embodiments, MCH receptor antagonists for use herein detectably inhibit MCH binding to MCHR1. Briefly, a competition assay is performed in which a MCH receptor preparation is incubated with labeled (*e.g.*, ^{125}I) MCH and unlabeled test compound. The MCH receptor used is preferably a mammalian MCHR1 or MCHR2, more preferably a human or monkey MCHR1 or MCHR2. The MCH receptor preparation may be, for example, a membrane preparation from HEK293 cells that recombinantly express a human MCH receptor (*e.g.*, Genbank Accession No. Z86090), monkey MCHR1 (such as the MCHR1 sequence provided in SEQ ID NO:1 of WO 03/060475), or human MCHR1/human beta-2-adrenergic chimeric receptor. Incubation with a MCH receptor antagonist results in a decrease in the amount of label bound to the MCH receptor preparation, relative to the amount of label bound in the absence of the antagonist. Preferably, a MCH receptor antagonist exhibits a K_i at a MCH receptor of less than 1 micromolar, binding specifically and with high affinity to a MCH receptor. More preferably, such a compound exhibits a K_i at a MCH receptor of less than 500 nM, 100 nM, 20 nM or 10 nM.

In certain embodiments, MCHR antagonists include substituted 1-benzyl-4-aryl piperazine and piperidine analogues, as described within pending US Patent Application No. 10/152,189, which published as US 2005-0065162 on March 24, 2005. The corresponding PCT application published as WO 02/094799 on November 28, 2002, and this disclosure is hereby incorporated herein by reference for its teaching of MCHR antagonists (pages 3-5, 20-25 and 74-107) and the preparation thereof (pages 29-42 and 50-73). Within other embodiments, MCH receptor antagonists for use as described herein are substituted benzimidazole analogues as described within pending U.S. Patent Application No. 10/399,499, filed January 9, 2003. The corresponding PCT application published

as WO 03/060475 on July 24, 2003, and this disclosure is hereby incorporated herein by reference for its teaching of MCH receptor antagonists (pages 2-5, Table I (pages 14-19) and Table II (pages 38-48) and the preparation thereof (pages 23-24 and 32-38). Within further embodiments, MCH receptor antagonists are as described within pending U.S. Patent Application No. 10/399,111, filed January 9, 2003. The corresponding PCT application published as WO 03/059289 on July 24, 2003, and this disclosure is hereby incorporated herein by reference for its teaching of MCH receptor antagonists (pages 3-4 and 31-50) and the preparation thereof (pages 19-20 and 28-31). Within further embodiments, MCH receptor antagonists include those described within U.S. Patent No. 6,569,861, which is hereby incorporated by reference for its teaching of phenylcycloalkylmethylamino and phenylalkenylamino MCH receptor antagonists (columns 3-9 and 18-19) and the preparation thereof (columns 16-18). Still further MCH receptor antagonists are described, for example, within the following published PCT applications: WO 03/097047, WO 03/087046, WO 03/087045, WO 03/087044, WO 03/072780, WO 03/070244, WO 03/047568, WO 03/045920, WO 03/045918, WO 03/045313, WO 03/035055, WO 03/033480, WO 03/015769, WO 03/028641, WO 03/013574, WO 03/004027, WO 02/089729, WO 02/083134, WO 02/076947, WO 02/076929, WO 02/057233, WO 02/051809, WO 02/10146, WO 02/06245, WO 02/04433, WO 01/87834, WO 01/82925, WO 01/57070, WO 01/21577 and WO 01/21169, as well as Japanese Application Publication Number 2001-226269. It will be apparent that the above are illustrative examples of MCH receptor antagonists, and are not intended to limit the scope of the present invention.

Representative second agents suitable for treating an addictive disorder include, for example, Methadone, LAAM (levo-alpha-acetyl-methadol), naltrexone (*e.g.*, ReVia™), ondansetron (*e.g.*, Zofran®), sertraline (*e.g.*, Zoloft®), fluoxetine (*e.g.*, Prozac®), diazepam (*e.g.*, Valium®) and chlordiazepoxide (*e.g.*, Librium), varenicline and buproprion (*e.g.*, Zyban® or Wellbutrin®). Other representative second agents for use within the pharmaceutical compositions provided herein include nicotine receptor partial agonists, opioid antagonists and/or dopaminergic agents.

Pharmaceutical compositions may be packaged for treating conditions responsive to CB1 modulation (*e.g.*, treatment of appetite disorder, obesity and/or addictive disorder, or other disorder indicated above). Packaged pharmaceutical preparations generally comprise a container holding a therapeutically effective amount of a pharmaceutical composition as described above and instructions (*e.g.*, labeling) indicating that the composition is to be used for treating a condition responsive to CB1 modulation in a patient. In certain embodiments, a packaged pharmaceutical preparation comprises one or more compounds provided herein and one or more additional agents in the same package, either in separate containers within the package or in the same container (*i.e.*, as a mixture). Preferred mixtures are formulated for oral administration (*e.g.*, as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the components are to be taken together for the treatment of an appetite disorder, obesity, an

addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder and/or bone loss.

METHODS OF USE

Within certain aspects, the present invention provides methods for treating a condition responsive to CB1 modulation in a patient and/or for appetite suppression. The patient may be afflicted with such a condition, or may be free of symptoms but considered at risk for developing such a condition. A condition is "responsive to CB1 modulation" if the condition or symptom(s) thereof are alleviated, attenuated, delayed or otherwise improved by modulation of CB1 activity. Such conditions include, for example, appetite disorders, obesity, addictive disorders, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, memory disorders, cognitive disorders, movement disorders and bone loss, as well as other disorders indicated above. In general, such methods comprise administering to the patient a therapeutically effective amount of at least one diaryl urea as provided herein.

It will be apparent that diaryl ureas provided herein may be administered alone or in combination with one or more additional agents that are suitable for treating the disorder of interest. Within combination therapy, the diaryl urea(s) and additional agent(s) may be present in the same pharmaceutical composition, or may be administered separately in either order. Representative additional agents for use in such methods include the second agents described above.

Suitable dosages for compounds provided herein (either alone or within such combination therapy) are generally as described above. Dosages and methods of administration of any additional agent(s) can be found, for example, in the manufacturer's instructions or in the *Physician's Desk Reference.* In certain embodiments, combination administration results in a reduction of the dosage of the additional agent required to produce a therapeutic effect (*i.e.,* a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of additional agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the agent without combination with a compound of Formula I. More preferably this dose is less than ¾, even more preferably less than ½, and highly preferably less than ¼ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the agent(s) when administered without combination administration as described herein. It will be apparent that the dose of compound as provided herein needed to achieve the desired effect may similarly be affected by the dose and potency of the additional agent.

Administration to the patient can be by way of any means discussed above, including oral, topical, nasal or transdermal administration, or intravenous, intramuscular, subcutaneous, intrathecal, epidural, intracerebroventrilcular or like injection. Oral administration is preferred in certain embodiments (*e.g.,* formulated as pills, capsules, tablets or the like).

Treatment regimens may vary depending on the compound used and the particular condition to be treated. In general, a dosage regimen of 4 times daily or less is preferred, with 1 or 2 times daily particularly preferred. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. Dosages are generally as described above; in general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented. For example, treatment of obesity is considered to be effective if it results in a statistically significant decrease in weight or BMI.

For combination therapy, pharmaceutical compositions may be formulated in single-dose units (*e.g.*, tablets or capsules). Each unit may contain both the diaryl urea and the second agent; alternatively, each unit may contain a single agent, with the units coadministered to achieve combination therapy. Within single-dose units, the diaryl urea and second agent (*e.g.*, MCH receptor antagonist) are present in therapeutically effective amounts (*i.e.*, an amount that results in a discernible benefit in a patient when the diaryl urea and second agent are administered contemporaneously and repeatedly at a prescribed frequency (*e.g.*, from 1 to 4 times per day for a period of weeks or months) to a patient. Such benefit(s) include those described above, such as decreased BMI, decreased appetite or food intake and/or weight loss. A therapeutically effective amount of second agent is an amount that results in such a discernible patient benefit when so administered, as compared to the patient benefit observed following administration of diaryl urea alone. Similarly, a therapeutically effective amount of diaryl urea is an amount that results in such a discernible patient benefit when so administered, as compared to the patient benefit observed following administration of second agent alone. "Contemporaneously," as used herein, refers to a time frame such that the second agent is present in a body fluid of a patient (at a therapeutic concentration) at the same time as the CB1 antagonist is present in the body fluid (at a therapeutic concentration). Contemporaneous administration is also referred to herein as "coadministration."

It will be apparent that the therapeutically effective amount in the context of combination therapy may be lower than the therapeutically effective amount for an agent administered alone. In certain embodiments, a therapeutically effective amount of second agent is lower than the amount that would need to be administered to effect a comparable patient benefit in the absence of diaryl urea. Within certain compositions and methods provided herein, at least an additive effect is observed (*i.e.*, the patient benefit is at least the sum of the benefits that would be achieved by the separate administration of the same amounts of second agent and diaryl urea).

In certain embodiments, the therapeutically effective amount of second agent is less than ¾, ½, ¼ or 10% of the maximum recommended dose for the MCHR antagonist (*i.e.*, the maximum dose

advised by the manufacturer or the U.S. Food and Drug Administration (FDA)). Similarly, in certain embodiments, a therapeutically effective amount of diaryl urea is lower than the amount that would need to be administered to effect a comparable patient benefit in the absence of second agent. In certain embodiments, the therapeutically effective amount of diaryl urea is less than ¾, ½, ¼ or 10% of the maximum recommended dose for the diaryl urea (*i.e.*, the maximum dose advised by the manufacturer or the FDA).

In further embodiments, the therapeutically effective amount of second agent is less than the minimum dose of the second agent proven effective in a United States clinical trial of the second agent, wherein the trial is conducted without coadministration of diaryl urea (*e.g.*, the therapeutically effective amount is less than 95%, less than 90%, less than 75% or less than 50% of the minimum dose proven effective in such a clinical trial). In other embodiments, the therapeutically effective amount of diaryl urea is lower than the minimum dose of the diaryl urea proven effective in a United States clinical trial of the diaryl urea, wherein the trial is conducted without coadministration of a second agent (*e.g.*, the therapeutically effective amount is less than 95%, less than 90%, less than 75% or less than 50% of the minimum dose proven effective in such a clinical trial). In still further such embodiments, both the second agent and the diaryl urea are employed at doses that are lower than the minimum dose proven effective in such clinical trials. The phrase "clinical trial," as used herein, refers to an experimental study in human subjects performed for purposes related to the development and submission of information under a federal law which regulates the manufacture, use or sale of drugs.

In other embodiments, the therapeutically effective amount of second agent is lower than the minimum marketed dose (for the patient's size) for use without coadministration of a second agent and/or the therapeutically effective amount of diaryl urea is lower than the minimum marketed dose (for the patient's size) for use without coadministration of a second agent. For example, the therapeutically effective amount of one or both of second agent and diaryl urea may be less than 95%, less than 90%, less than 75% or less than 50% of the minimum marketed dose. In certain such embodiments, the patient is a non-human animal, such as a companion animal (*e.g.*, a dog or cat).

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the diaryl ureas provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of CB1 (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to CB1, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize CB1 receptors in living subjects. For example, a compound may be

labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of CB1 in the sample. Detection assays, including receptor autoradiography (receptor mapping) of CB1 in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Diaryl ureas provided herein may further be used within assays for the identification of other non-competitive antagonists of CB1. In general, such assays are standard competition binding assays, in which a labeled compound as provided herein is displaced by a test compound. Briefly, such assays are performed by: (a) contacting CB1 with a labeled (*e.g.*, radiolabeled) diaryl urea and a test compound, under conditions that permit binding of the diaryl urea to CB1 (b) removing unbound labeled diaryl urea and unbound test compound; (c) detecting a signal that corresponds to the amount of bound, labeled diaryl urea; and (d) comparing the signal to a reference signal that corresponds to the amount of bound labeled diaryl urea in a similar assay performed in the absence of test compound. In practice, the reference signal and the signal described in step (c) are generally obtained simultaneously (*e.g.*, the assays are performed in different wells of the same plate); in addition, multiple concentrations of test compound are generally assayed. Non-competitive antagonist activity can be confirmed for test compounds that decrease the amount of bound, labeled diaryl urea using procedures described herein.

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

EXAMPLES

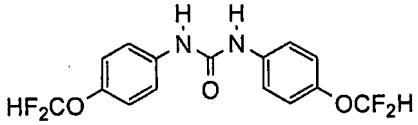
Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Micromass, Beverly MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector, and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI. MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and

AutoLynx™ processing is used for data collection and analysis. MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 min.

Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% methanol with 0.05% TFA; Mobile Phase B - 5% water, 95% methanol with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

EXAMPLE 1. PREPARATION OF REPRESENTATIVE CB1 ANTAGONISTS

This Example illustrates the preparation of the representative diaryl urea N,N'-bis[4-(difluoromethoxy)phenyl]urea.

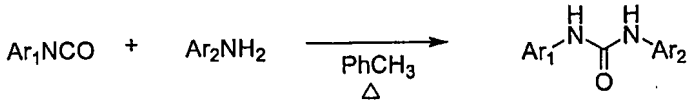


A solution of 4-difluoromethoxyaniline (258 mg, 1.62 mmol) and 4-difluoromethoxyphenyl isocyanate (300 mg, 1.62 mmol) in toluene (8.1 mL) is heated at 70°C for 1.5 h. The resulting white solid is collected by suction filtration and dried with suction for 30 min to obtain N,N'-bis[4-(difluoromethoxy)phenyl]urea as a white solid. ^{1}H NMR: (CD_3OD) 7.45 (dd, 4H), 7.09 (dd, 4H), 6.91(dt, 2H, J_1 = 56 Hz).

EXAMPLE 2. HIGH SPEED SYNTHESIS OF REPRESENTATIVE CB1 ANTAGONISTS

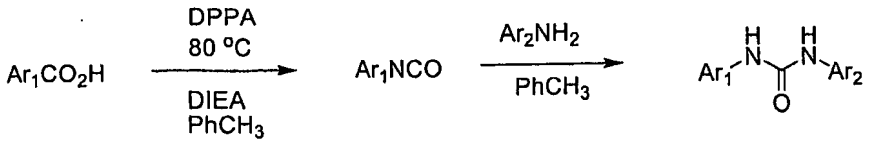
This Example illustrates the high speed synthesis of representative diaryl ureas.

PROTOCOL A.



Aryl isocyanate (0.15 mL of 0.2 M in toluene) is added to a reaction vial followed by aryl amine (0.1 mL of 0.2M in toluene). The reaction vessel is sealed and heated at 70°C with agitation for 16 h. A solution of N-(3-aminopropyl)morpholine (0.5 mL of 0.2 M in ethyl acetate) is added and the reaction is heated at 70°C for 1 h. The reaction is cooled, diluted with ethyl acetate (0.3 mL) and eluted through a silica gel SPE cartridge with ethyl acetate (3.0 mL). The eluent is evaporated, weighed and diluted to a concentration of 10 mM in DMSO. Purity is assessed using LC/MS.

PROTOCOL B (CURTIUS REARRANGEMENT).



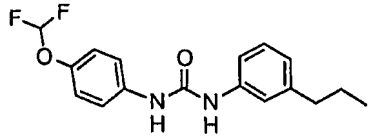
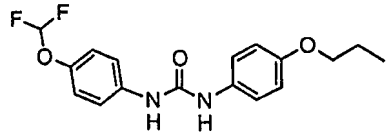
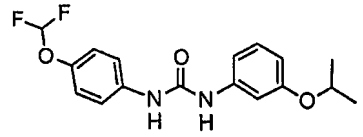
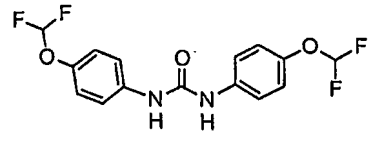
To a solution of aryl carboxylic acid (0.15 mL of 0.2 M in toluene/5% vv DIEA) is added diphenylphosporyl azide (0.12 mL of 2M in toluene). The reaction vessel is sealed and heated at 80°C for 4 h with agitation. The reaction mixture is cooled, aryl amine (0.1 mL of 0.2 M in toluene) is added and the reaction mixture is agitated at room temperature for 1 h. The reaction mixture is partitioned between ethyl acetate (0.5 mL) and 1 N NaOH. The upper phase is removed and purified on a SCX cartridge eluting with 25% MeOH/EtOAc (3 mL). The eluent is evaporated, weighed and diluted to a concentration of 10 mM in DMSO. Purity is assessed using LC/MS.

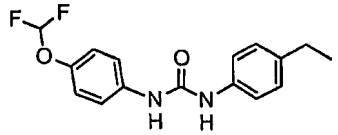
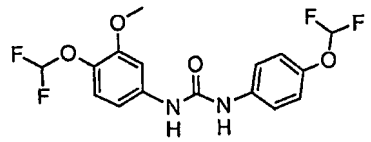
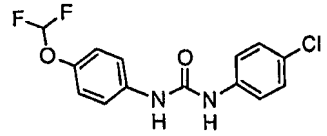
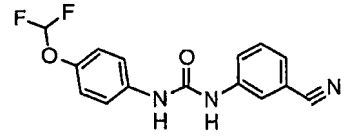
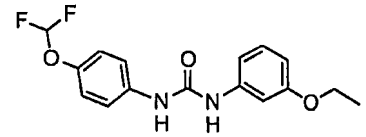
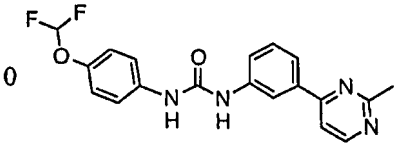
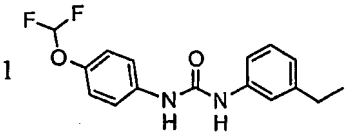
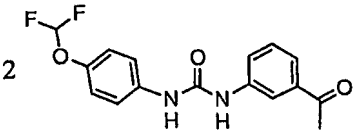
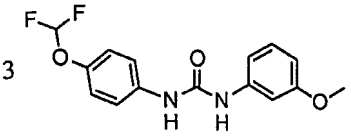
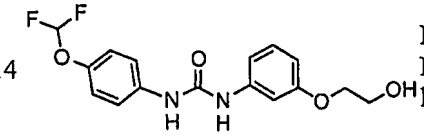
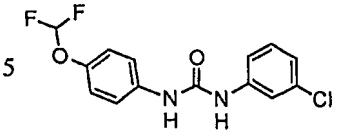
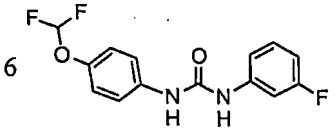
EXAMPLE 3. ADDITIONAL REPRESENTATIVE CB1 ANTAGONISTS

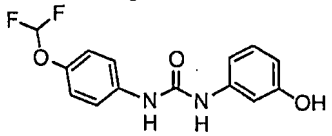
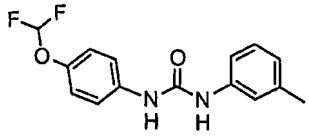
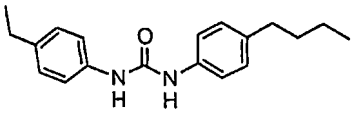
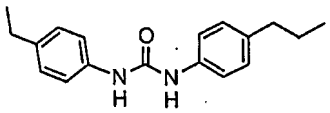
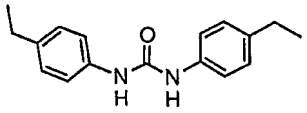
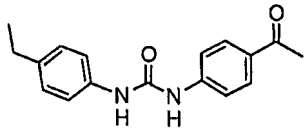
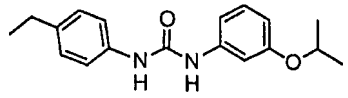
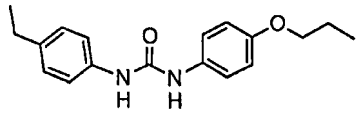
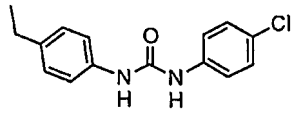
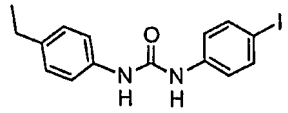
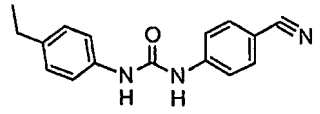
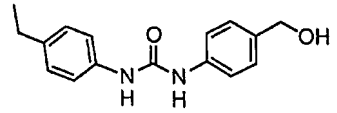
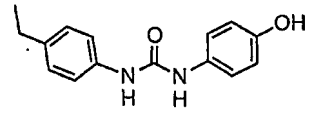
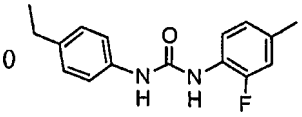
Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Tables I - III are prepared using such methods. A "*" in the column headed "IC_{50}" indicates that the IC_{50} at CB1, determined as described in Example 8, herein, is 2 micromolar or less. "Ret. time" or "R.T." is the retention time in minutes and mass spectroscopy data (MS) is generated as described above and is presented as M+1.

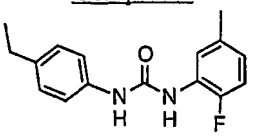
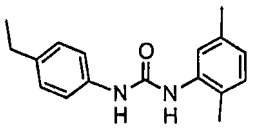
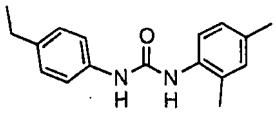
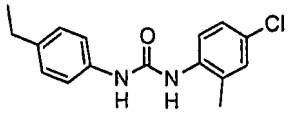
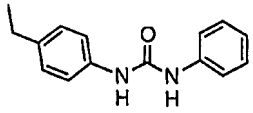
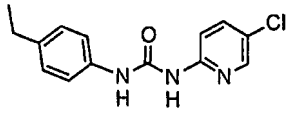
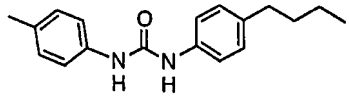
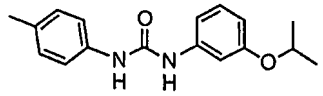
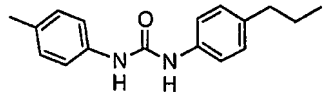
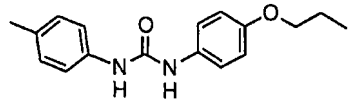
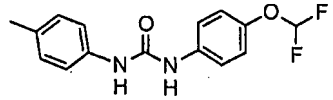
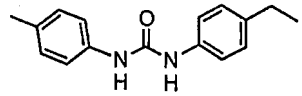
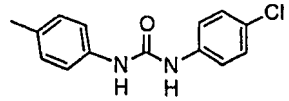
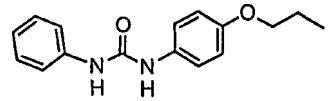
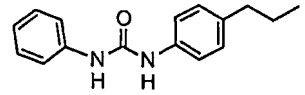
Table I

Representative CB1 Antagonists

	Compound	Name	Ret. time	MS (M+1)	IC_{50}
1		N-[4-(difluoromethoxy)phenyl]-N'-(4-propylphenyl)urea	1.35	321.1	
2		N-[4-(difluoromethoxy)phenyl]-N'-(4-propoxyphenyl)urea	1.31	337.1	
3		N-[4-(difluoromethoxy)phenyl]-N'-(3-isopropoxyphenyl)urea	1.3	337.1	
4		N,N'-bis[4-(difluoromethoxy)phenyl]urea	1.28	345.1	*

	Compound	Name	Ret. time	MS (M+1)	IC_{50}
5		N-[4-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea	1.31	307.1	*
6		N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.28	375.1	*
7		N-(4-chlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.3	313.1	
8		N-(3-cyanophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.26	304.1	*
9		N-[4-(difluoromethoxy)phenyl]-N'-(3-ethoxyphenyl)urea	1.29	323.1	*
10		N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea	1.27	371.1	*
11		N-[4-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea	1.32	307.1	*
12		N-(3-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.25	321.1	*
13		N-[4-(difluoromethoxy)phenyl]-N'-(3-methoxyphenyl)urea	1.26	309.1	
14		N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-hydroxyethoxy)phenyl]urea			*
15		N-(3-chlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.31	313.1	*
16		N-[4-(difluoromethoxy)phenyl]-N'-(3-fluorophenyl)urea	1.28	297.1	*

Compound	Name	Ret. time	MS (M+1)	IC_{50}
17 	N-[4-(difluoromethoxy)phenyl]-N'-(3-hydroxyphenyl)urea	1.21	295.1	*
18 	N-[4-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea	1.29	293.1	*
19 	N-(4-butylphenyl)-N'-(4-ethylphenyl)urea	1.42	297.2	
20 	N-(4-ethylphenyl)-N'-(4-propylphenyl)urea	1.38	283.2	*
21 	N,N'-bis(4-ethylphenyl)urea	1.36	269.2	*
22 	N-(4-acetylphenyl)-N'-(4-ethylphenyl)urea	1.3	283.1	*
23 	N-(4-ethylphenyl)-N'-(3-isopropoxyphenyl)urea	1.36	299.2	*
24 	N-(4-ethylphenyl)-N'-(4-propoxyphenyl)urea	1.35	299.2	*
25 	N-(4-chlorophenyl)-N'-(4-ethylphenyl)urea	1.35	275.1	*
26 	N-(4-ethylphenyl)-N'-(4-iodophenyl)urea	1.38	367.0	
27 	N-(4-cyanophenyl)-N'-(4-ethylphenyl)urea	1.31	266.1	*
28 	N-(4-ethylphenyl)-N'-[4-(hydroxymethyl)phenyl]urea	1.25	271.1	*
29 	N-(4-ethylphenyl)-N'-(4-hydroxyphenyl)urea	1.23	257.1	*
30 	N-(4-ethylphenyl)-N'-(2-fluoro-4-methylphenyl)urea	1.35	273.1	

Compound	Name	Ret. time	MS (M+1)	IC_{50}
31 	N-(4-ethylphenyl)-N'-(2-fluoro-5-methylphenyl)urea	1.36	273.1	
32 	N-(2,5-dimethylphenyl)-N'-(4-ethylphenyl)urea			
33 	N-(2,4-dimethylphenyl)-N'-(4-ethylphenyl)urea	1.34	269.2	
34 	N-(4-chloro-2-methylphenyl)-N'-(4-ethylphenyl)urea	1.37	289.1	
35 	N-(4-ethylphenyl)-N'-phenylurea	1.17	241.2	*
36 	N-(5-chloropyridin-2-yl)-N'-(4-ethylphenyl)urea	1.4	276.1	
37 	N-(4-butylphenyl)-N'-(4-methylphenyl)urea	1.39	283.2	*
38 	N-(3-isopropoxyphenyl)-N'-(4-methylphenyl)urea	1.31	285.1	*
39 	N-(4-methylphenyl)-N'-(4-propylphenyl)urea	1.36	269.2	*
40 	N-(4-methylphenyl)-N'-(4-propoxyphenyl)urea	1.33	285.1	*
41 	N-[4-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea	1.28	293.1	*
42 	N-(4-ethylphenyl)-N'-(4-methylphenyl)urea	1.33	255.1	*
43 	N-(4-chlorophenyl)-N'-(4-methylphenyl)urea	1.32	261.1	*
44 	N-phenyl-N'-(4-propoxyphenyl)urea	1.29	271.1	*
45 	N-phenyl-N'-(4-propylphenyl)urea	1.34	255.1	*

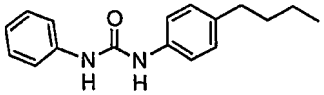
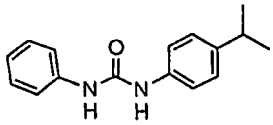
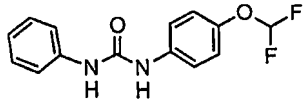
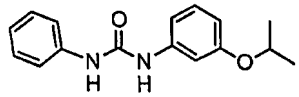
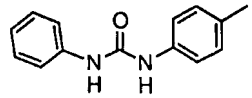
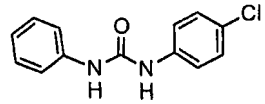
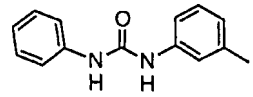
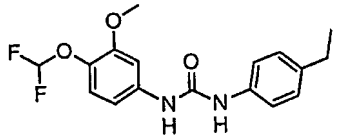
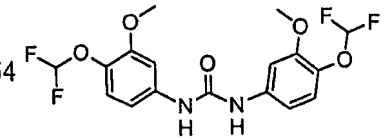
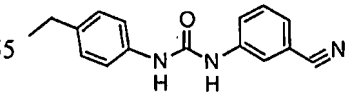
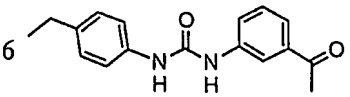
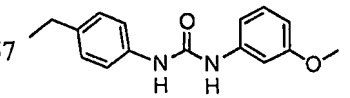
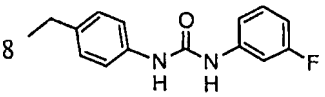
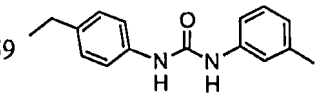
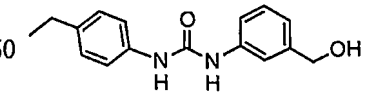
Compound	Name	Ret. time	MS (M+1)	IC_{50}
46 	N-(4-butylphenyl)-N'-phenylurea	1.37	269.2	*
47 	N-(4-isopropylphenyl)-N'-phenylurea	1.33	255.1	*
48 	N-[4-(difluoromethoxy)phenyl]-N'-phenylurea	1.26	279.1	*
49 	N-(3-isopropoxyphenyl)-N'-phenylurea	1.3	271.1	*
50 	N-(4-methylphenyl)-N'-phenylurea			
51 	N-(4-chlorophenyl)-N'-phenylurea	1.29	247.1	
52 	N-(3-methylphenyl)-N'-phenylurea			
53 	N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-ethylphenyl)urea	1.32	337.1	
54 	N,N'-bis[4-(difluoromethoxy)-3-methoxyphenyl]urea	1.28	405.1	*
55 	N-(3-cyanophenyl)-N'-(4-ethylphenyl)urea	1.29	266.1	*
56 	N-(3-acetylphenyl)-N'-(4-ethylphenyl)urea	1.29	283.1	*
57 	N-(4-ethylphenyl)-N'-(3-methoxyphenyl)urea	1.3	271.1	*
58 	N-(4-ethylphenyl)-N'-(3-fluorophenyl)urea	1.31	259.1	*
59 	N-(4-ethylphenyl)-N'-(3-methylphenyl)urea	1.33	255.1	*
60 	N-(4-ethylphenyl)-N'-[3-(hydroxymethyl)phenyl]urea	1.25	271.1	

Table II

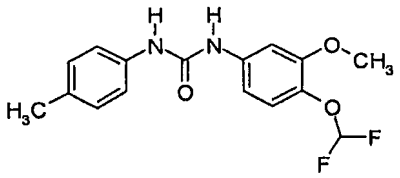
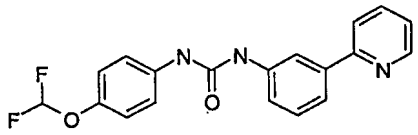
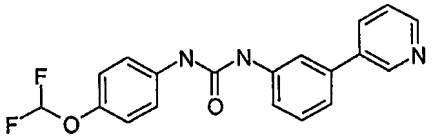
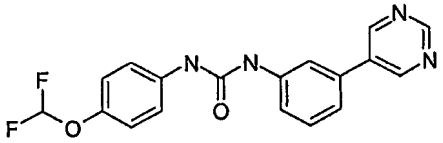
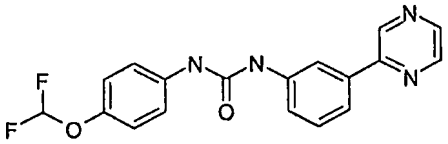
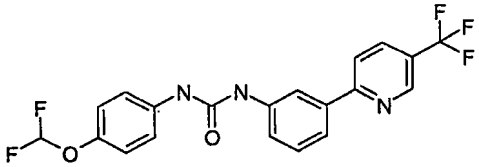
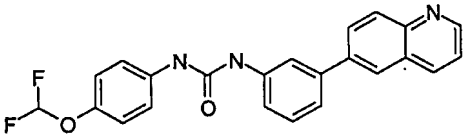
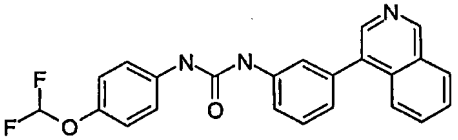
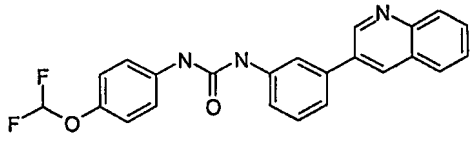
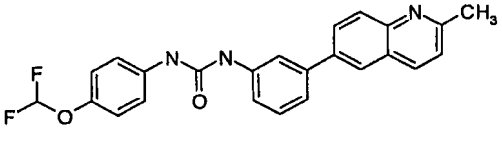
	Compound	Name	R.T.	MS	IC_{50}
61		N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-methylphenyl)urea	1.28	323.1	*
62		N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-2-ylphenyl)urea	1.18	356.1	*
63		N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-3-ylphenyl)urea	1.18	356.1	*
64		N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrimidin-5-ylphenyl)urea	1.25	357.1	*
65		N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrazin-2-ylphenyl)urea	1.26	357.2	*
66		N-[4-(difluoromethoxy)phenyl]-N'-{3-[5-(trifluoromethyl)pyridin-2-yl]phenyl}urea	1.35	424.1	*
67		N-[4-(difluoromethoxy)phenyl]-N'-(3-quinolin-6-ylphenyl)urea	1.23	406.2	*
68		N-[4-(difluoromethoxy)phenyl]-N'-(3-isoquinolin-4-ylphenyl)urea	1.22	406.2	*
69		N-[4-(difluoromethoxy)phenyl]-N'-(3-quinolin-3-ylphenyl)urea	1.26	406.2	*
70		N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-methylquinolin-6-yl)phenyl]urea	1.21	420.2	*

Table II

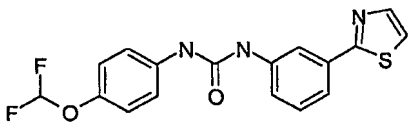
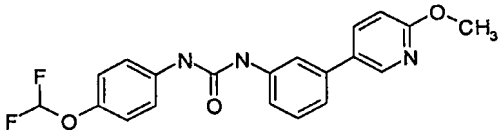
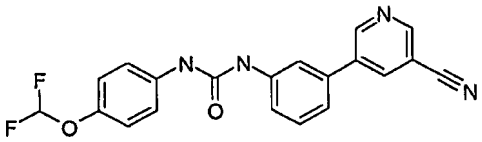
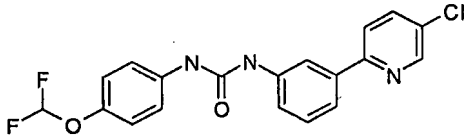
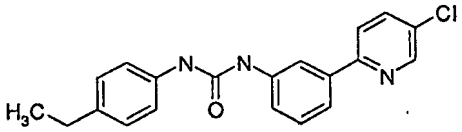
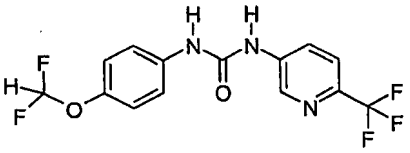
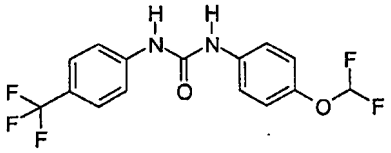
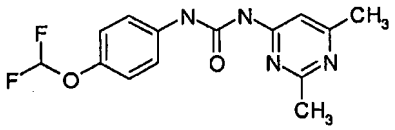
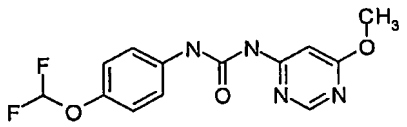
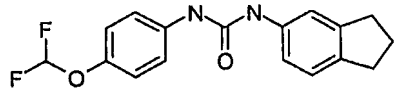
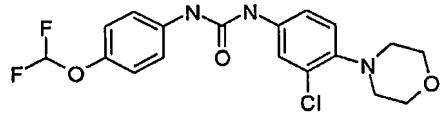
	Compound	Name	R.T.	MS	IC_{50}
71		N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-thiazol-2-yl)phenyl]urea	1.29	362.1	*
72		N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-methoxypyridin-3-yl)phenyl]urea	1.32	386.2	*
73		N-[3-(5-cyanopyridin-3-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea			*
74		N-[3-(5-chloropyridin-2-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.34	390.1	*
75		N-[3-(5-chloropyridin-2-yl)phenyl]-N'-(4-ethylphenyl)urea	1.37	352.1	*
76		N-[4-(difluoromethoxy)phenyl]-N'-[6-(trifluoromethyl)pyridin-3-yl]urea	1.29	348.1	*
77		N-[4-(difluoromethoxy)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea	1.33	347.1	*
78		N-[4-(difluoromethoxy)phenyl]-N'-(2,6-dimethylpyrimidin-4-yl)urea	1.16	309.1	*
79		N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyrimidin-4-yl)urea	1.29	311.1	*
80		N-[4-(difluoromethoxy)phenyl]-N'-(2,3-dihydro-1H-inden-5-yl)urea			*
81		N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.31	398.1	*

Table II

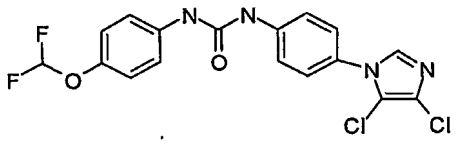
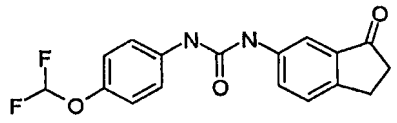
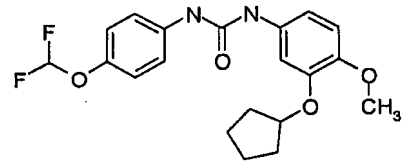
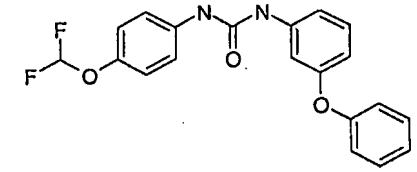
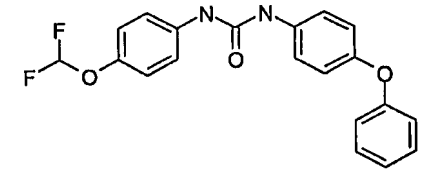
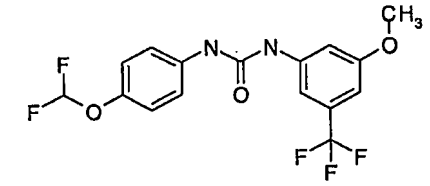
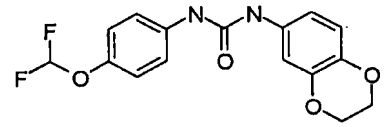
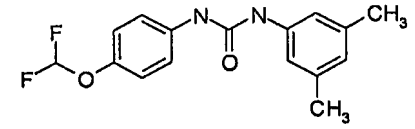
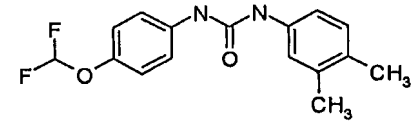
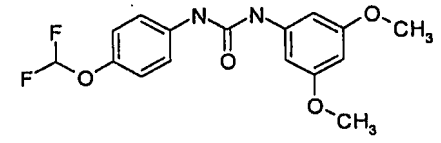
	Compound	Name	R.T.	MS	IC_{50}
82		N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.33	413.0	*
83		N-[4-(difluoromethoxy)phenyl]-N'-(3-oxo-2,3-dihydro-1H-inden-5-yl)urea	1.26	333.1	*
84		N-[3-(cyclopentyloxy)-4-methoxyphenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.33	393.2	*
85		N-[4-(difluoromethoxy)phenyl]-N'-(3-phenoxyphenyl)urea	1.36	371.1	*
86		N-[4-(difluoromethoxy)phenyl]-N'-(4-phenoxyphenyl)urea	1.35	371.1	*
87		N-[4-(difluoromethoxy)phenyl]-N'-[3-methoxy-5-(trifluoromethyl)phenyl]urea	1.34	377.1	*
88		N-[4-(difluoromethoxy)phenyl]-N'-(2,3-dihydro-1,4-benzodioxin-6-yl)urea	1.25	337.1	*
89		N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethylphenyl)urea	1.33	307.1	*
90		N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethylphenyl)urea	1.32	307.1	*
91		N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethoxyphenyl)urea	1.28	339.1	*

Table II

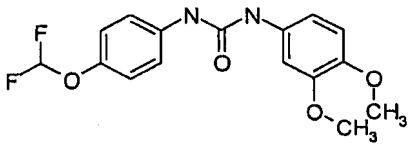
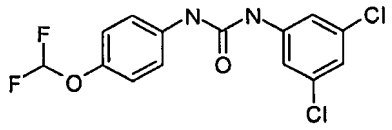
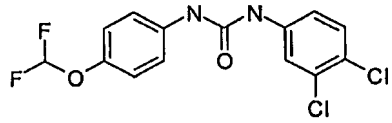
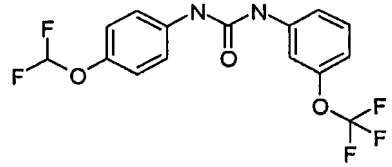
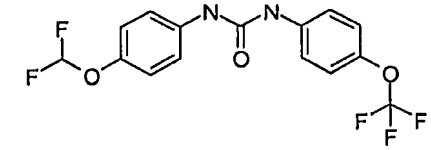
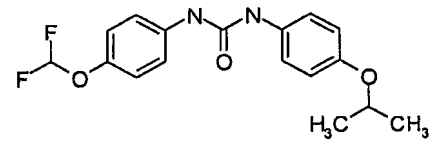
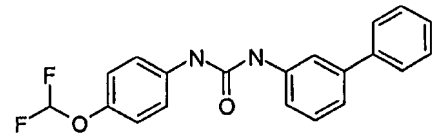
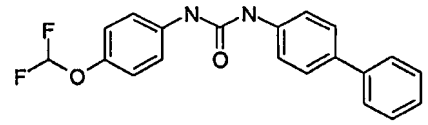
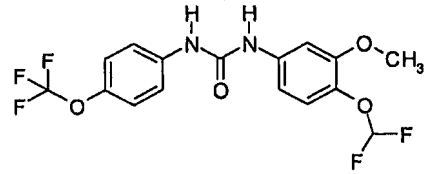
	Compound	Name	R.T.	MS	IC_{50}
92		N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethoxyphenyl)urea	1.23	339.1	*
93		N-(3,5-dichlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.39	347.1	*
94		N-(3,4-dichlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.37	359.3	*
95		N-[4-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea	1.34	363.1	*
96		N-[4-(difluoromethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea	1.34	363.1	*
97		N-[4-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea	1.3	337.1	*
98		N-biphenyl-3-yl-N'-[4-(difluoromethoxy)phenyl]urea	1.35	359.3	*
99		N-biphenyl-4-yl-N'-[4-(difluoromethoxy)phenyl]urea	1.36	359.3	*
100		N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(trifluoromethoxy)phenyl]urea	1.34	393.1	*

Table II

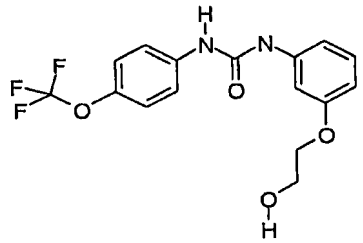
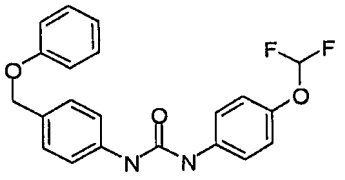
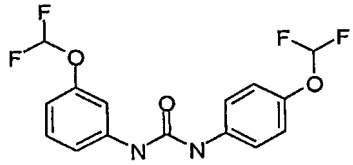
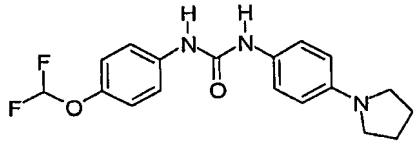
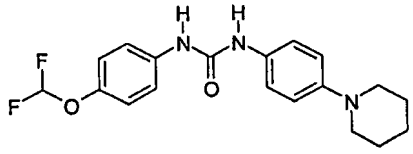
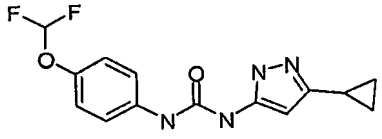
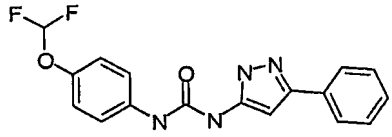
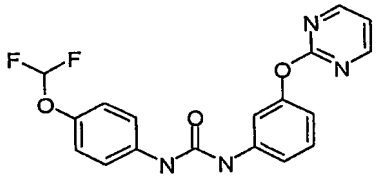
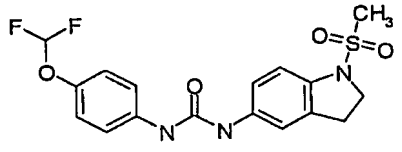
Compound	Name	R.T.	MS	IC_{50}
101 	N-[3-(2-hydroxyethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea	1.28	357.1	*
102 	N-[4-(difluoromethoxy)phenyl]-N'-[4-(phenoxymethyl)phenyl]urea			*
103 	N-[3-(difluoromethoxy)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.28	345.1	*
104 	N-[4-(difluoromethoxy)phenyl]-N'-(4-pyrrolidin-1-ylphenyl)urea	1.17	348.1	*
105 	N-[4-(difluoromethoxy)phenyl]-N'-(4-piperidin-1-ylphenyl)urea	1.16	362.2	*
106 	N-(3-cyclopropyl-1H-pyrazol-5-yl)-N'-[4-(difluoromethoxy)phenyl]urea	1.22	309.1	*
107 	N-[4-(difluoromethoxy)phenyl]-N'-(3-phenyl-1H-pyrazol-5-yl)urea			*
108 	N-[4-(difluoromethoxy)phenyl]-N'-[3-(pyrimidin-2-yloxy)phenyl]urea	1.23	373.1	*
109 	N-[4-(difluoromethoxy)phenyl]-N'-[1-(methylsulfonyl)-2,3-dihydro-1H-indol-5-yl]urea	1.23	398.1	*

Table II

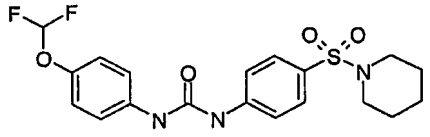
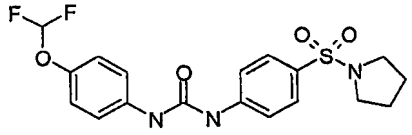
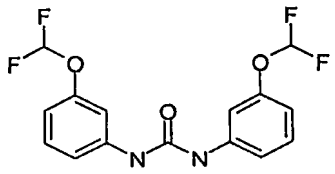
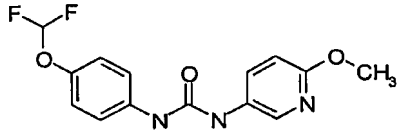
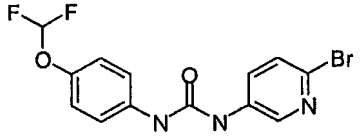
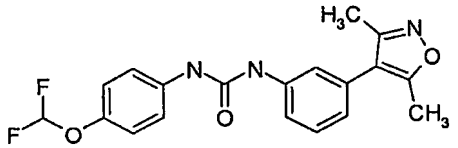
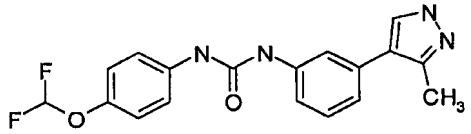
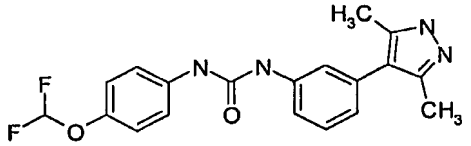
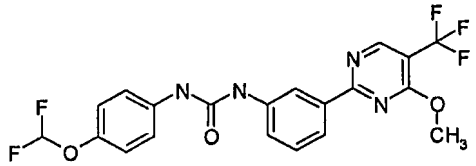
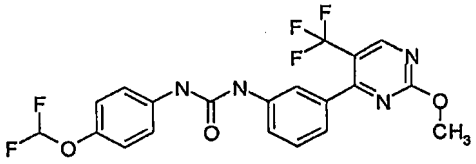
	Compound	Name	R.T.	MS	IC_{50}
110		N-[4-(difluoromethoxy)phenyl]-N'-[4-(piperidin-1-ylsulfonyl)phenyl]urea			*
111		N-[4-(difluoromethoxy)phenyl]-N'-[4-(pyrrolidin-1-ylsulfonyl)phenyl]urea	1.27	412.1	*
112		N,N'-bis[3-(difluoromethoxy)phenyl]urea	1.29	345.1	*
113		N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyridin-3-yl)urea	1.23	310.1	*
114		N-(6-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea	1.28	360.0	*
115		N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea	1.3	374.1	*
116		N-[4-(difluoromethoxy)phenyl]-N'-[3-(3-methyl-1H-pyrazol-4-yl)phenyl]urea			*
117		N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]urea	1.22	373.1	*
118		N-[4-(difluoromethoxy)phenyl]-N'-{3-[4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl]phenyl}urea			*
119		N-[4-(difluoromethoxy)phenyl]-N'-{3-[2-methoxy-5-(trifluoromethyl)pyrimidin-4-yl]phenyl}urea			*

Table II

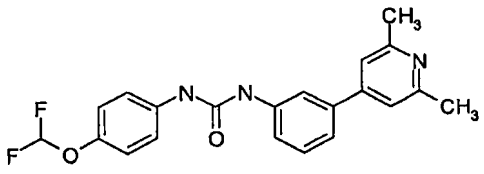
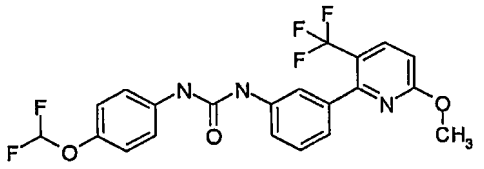
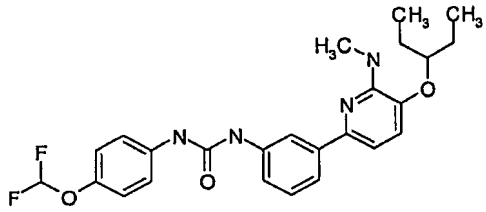
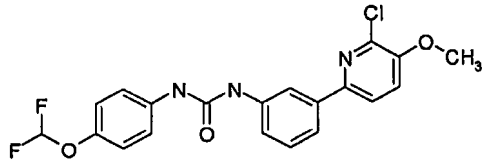
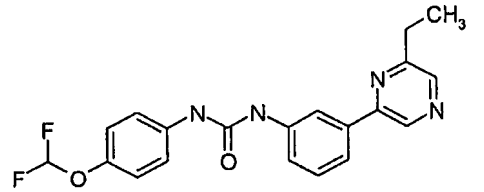
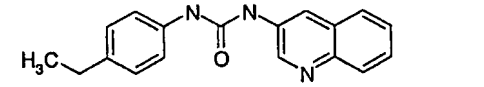
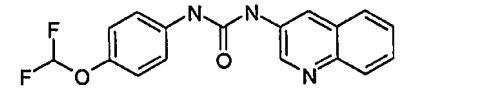
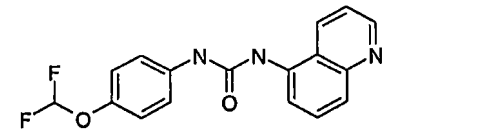
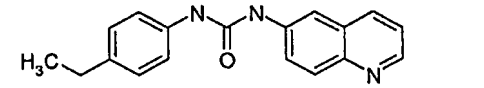
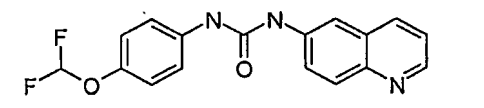
	Compound	Name	R.T.	MS	IC_{50}
120		N-[4-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea			*
121		N-[4-(difluoromethoxy)phenyl]-N'-{3-[6-methoxy-3-(trifluoromethyl)pyridin-2-yl]phenyl}urea			*
122		N-[4-(difluoromethoxy)phenyl]-N'-{3-[5-(1-ethylpropoxy)-6-(methylamino)pyridin-2-yl]phenyl}urea			*
123		N-[3-(6-chloro-5-methoxypyridin-2-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea	1.33	420.1	*
124		N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-ethylpyrazin-2-yl)phenyl]urea	1.33	385.1	*
125		N-(4-ethylphenyl)-N'-quinolin-3-ylurea	1.27	292.1	*
126		N-[4-(difluoromethoxy)phenyl]-N'-quinolin-3-ylurea	1.22	330.1	*
127		N-[4-(difluoromethoxy)phenyl]-N'-quinolin-5-ylurea	1.15	330.1	
128		N-(4-ethylphenyl)-N'-quinolin-6-ylurea	1.21	292.1	*
129		N-[4-(difluoromethoxy)phenyl]-N'-quinolin-6-ylurea	1.16	330.1	*

Table II

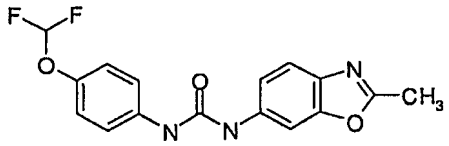
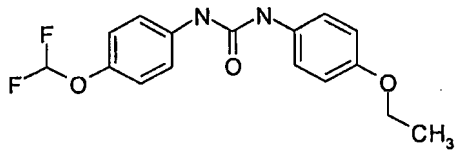
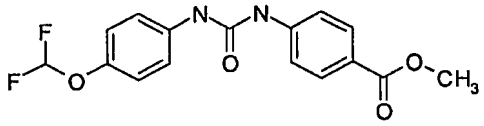
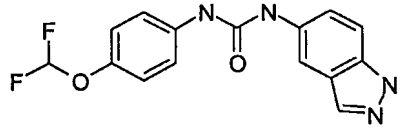
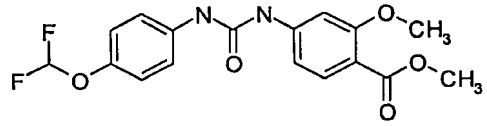
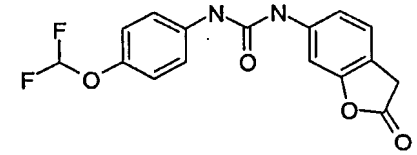
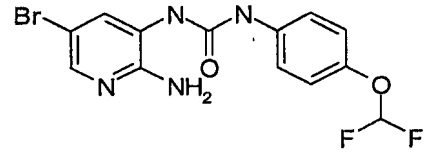
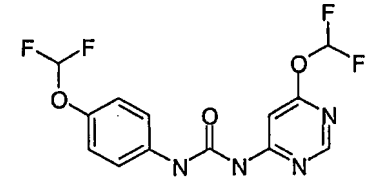
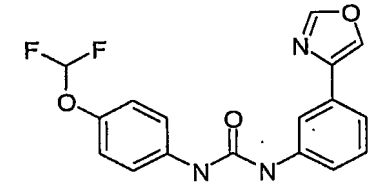
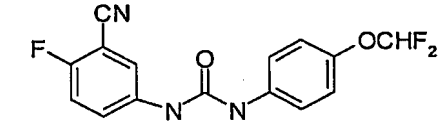
	Compound	Name	R.T.	MS	IC_{50}
130		N-[4-(difluoromethoxy)phenyl]-N'-(2-methyl-1,3-benzoxazol-6-yl)urea	1.26	334.1	*
131		N-[4-(difluoromethoxy)phenyl]-N'-(4-ethoxyphenyl)urea	1.29	323.1	*
132		methyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.28	337.1	*
133		N-[4-(difluoromethoxy)phenyl]-N'-1H-indazol-5-ylurea			*
134		methyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]-2-methoxybenzoate	1.28	345.1	*
135		N-[4-(difluoromethoxy)phenyl]-N'-(2-oxo-2,3-dihydro-1-benzofuran-6-yl)urea	1.23	335.1	*
136		N-(2-amino-5-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea	1.21	375.0	*
137		N-[4-(difluoromethoxy)phenyl]-N'-[6-(difluoromethoxy)pyrimidin-4-yl]urea	1.32	347.1	*
138		N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-oxazol-4-yl)phenyl]urea	1.27	346.1	*
139		N-(3-cyano-4-fluorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.27	322.1	*

Table II

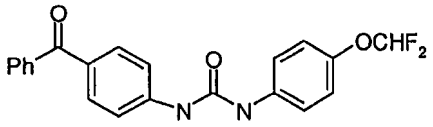
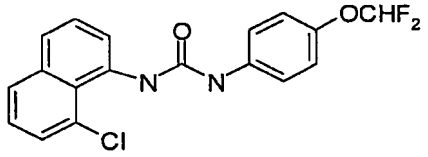
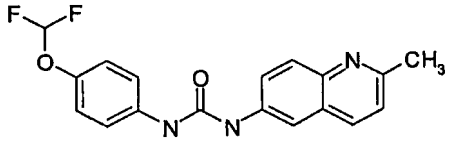
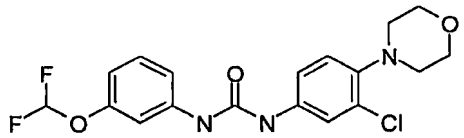
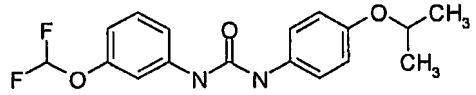
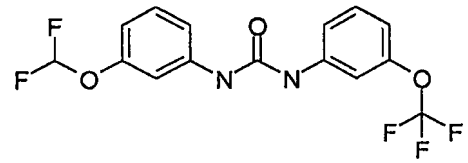
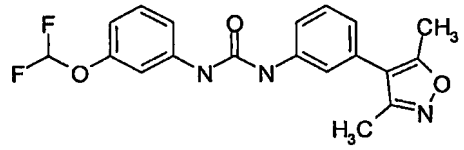
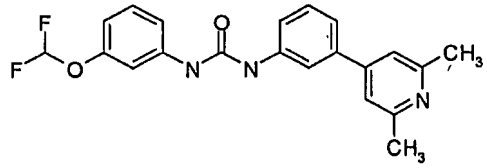
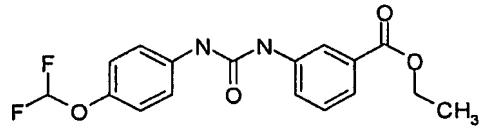
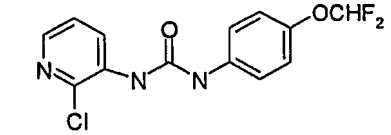
	Compound	Name	R.T.	MS	IC_{50}
140		N-(4-benzoylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.33	383.1	*
141		N-(8-chloro-1-naphthyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.37	359.3	*
142		N-[4-(difluoromethoxy)phenyl]-N'-(2-methylquinolin-6-yl)urea	1.16	344.1	*
143		N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.31	398.1	*
144		N-[3-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea			*
145		N-[3-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea	1.34	363.0	*
146		N-[3-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea	1.3	374.1	*
147		N-[3-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea			*
148		ethyl 3-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate			*
149		N-(2-chloropyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea	1.26	314.0	*

Table II

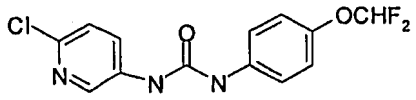
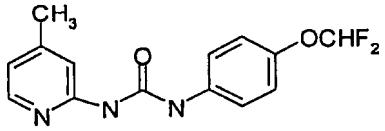
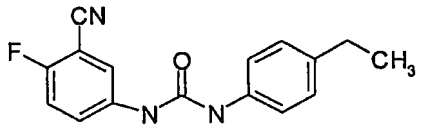
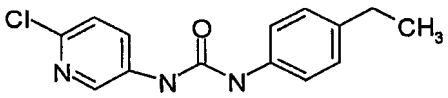
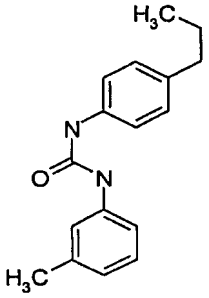
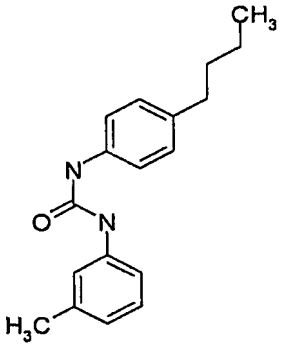
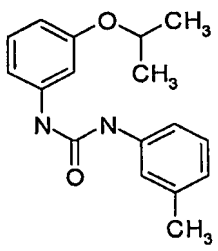
	Compound	Name	R.T.	MS	IC_{50}
150		N-(6-chloropyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea	1.27	314.0	*
151		N-[4-(difluoromethoxy)phenyl]-N'-(4-methylpyridin-2-yl)urea	1.17	294.1	*
152		N-(3-cyano-4-fluorophenyl)-N'-(4-ethylphenyl)urea	1.24	284.1	*
153		N-(6-chloropyridin-3-yl)-N'-(4-ethylphenyl)urea	1.23	276.1	*
154		N-(3-methylphenyl)-N'-(4-propylphenyl)urea	1.33	269.2	*
155		N-(4-butylphenyl)-N'-(3-methylphenyl)urea	1.36	283.2	*
156		N-(3-isopropoxyphenyl)-N'-(3-methylphenyl)urea	1.29	285.2	*

Table II

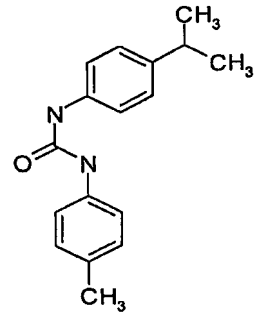
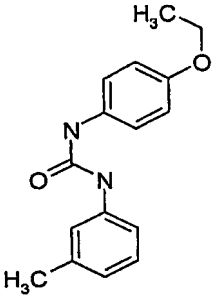
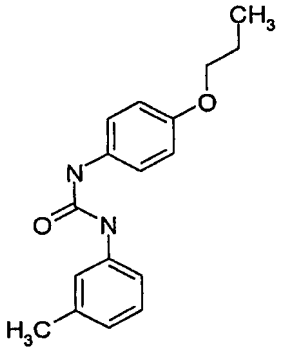
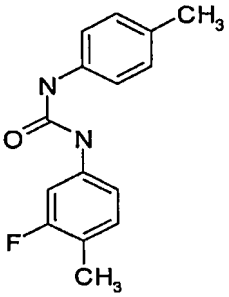
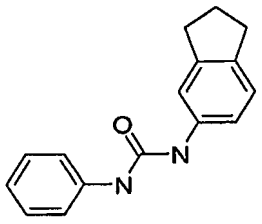
Compound	Name	R.T.	MS	IC_{50}
157 	N-(4-isopropylphenyl)-N'-(4-methylphenyl)urea	1.32	269.2	*
158 	N-(4-ethoxyphenyl)-N'-(3-methylphenyl)urea	1.26	271.2	*
159 	N-(3-methylphenyl)-N'-(4-propoxyphenyl)urea	1.3	285.2	*
160 	N-(3-fluoro-4-methylphenyl)-N'-(4-methylphenyl)urea	1.29	259.2	*
161 	N-(2,3-dihydro-1H-inden-5-yl)-N'-phenylurea	1.28	253.2	*

Table II

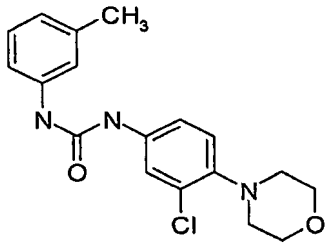
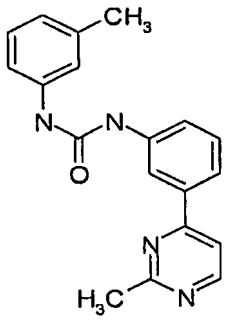
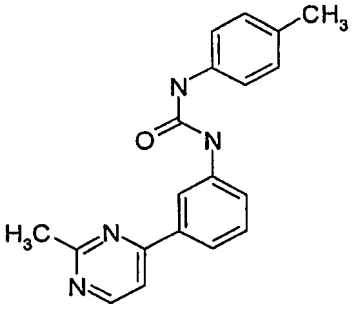
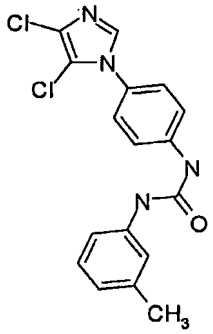
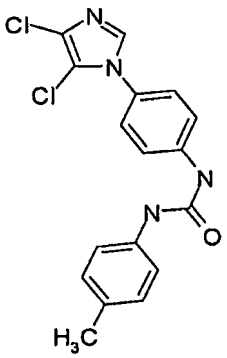
Compound	Name	R.T.	MS	IC_{50}
162 	N-(3-chloro-4-morpholin-4-ylphenyl)-N'-(3-methylphenyl)urea	1.23	346.2	*
163 	N-(3-methylphenyl)-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea	1.2	319.2	*
164 	N-(4-methylphenyl)-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea	1.2	319.2	*
165 	N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-(3-methylphenyl)urea	1.26	361.1	*
166 	N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-(4-methylphenyl)urea	1.25	361.1	*

Table II

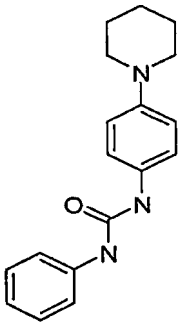
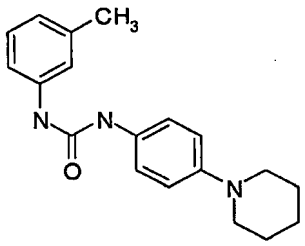
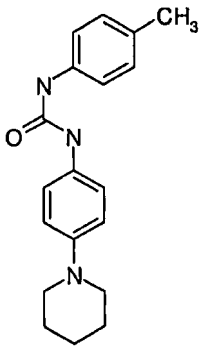
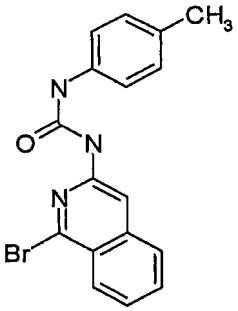
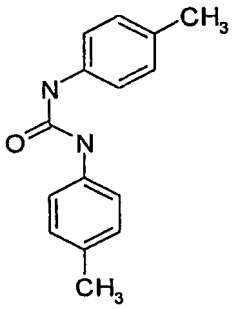
	Compound	Name	R.T.	MS	IC_{50}
167		N-phenyl-N'-(4-piperidin-1-ylphenyl)urea	1.05	296.2	*
168		N-(3-methylphenyl)-N'-(4-piperidin-1-ylphenyl)urea	1.08	310.2	*
169		N-(4-methylphenyl)-N'-(4-piperidin-1-ylphenyl)urea	1.08	310.2	*
170		N-(1-bromoisoquinolin-3-yl)-N'-(4-methylphenyl)urea			*
171		N,N'-bis(4-methylphenyl)urea	1.22	241.2	*

Table II

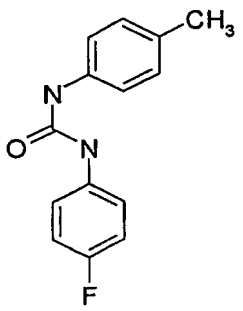
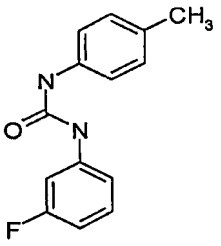
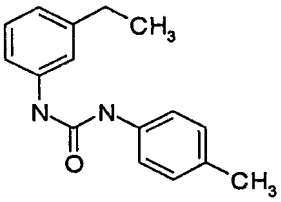
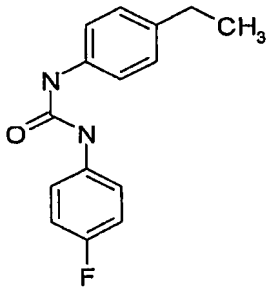
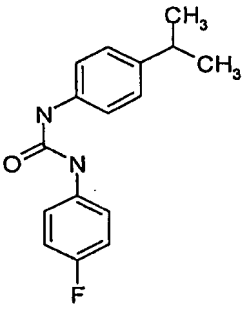
Compound	Name	R.T.	MS	IC_{50}
172 	N-(4-fluorophenyl)-N'-(4-methylphenyl)urea	1.2	245.1	*
173 	N-(3-fluorophenyl)-N'-(4-methylphenyl)urea	1.22	245.2	*
174 	N-(3-ethylphenyl)-N'-(4-methylphenyl)urea	1.25	255.2	*
175 	N-(4-ethylphenyl)-N'-(4-fluorophenyl)urea	1.24	259.2	*
176 	N-(4-fluorophenyl)-N'-(4-isopropylphenyl)urea	1.26	273.2	*

Table II

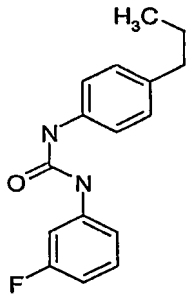
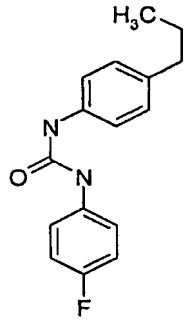
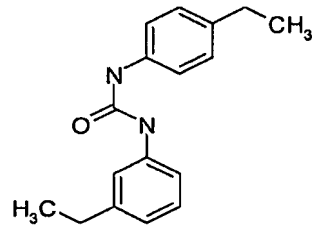
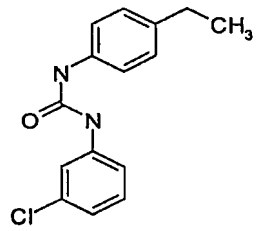
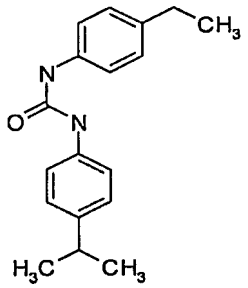
Compound	Name	R.T.	MS	IC_{50}
177 	N-(3-fluorophenyl)-N'-(4-propylphenyl)urea	1.28	273.2	*
178 	N-(4-fluorophenyl)-N'-(4-propylphenyl)urea	1.28	273.2	*
179 	N-(3-ethylphenyl)-N'-(4-ethylphenyl)urea	1.37	269.2	*
180 	N-(3-chlorophenyl)-N'-(4-ethylphenyl)urea	1.35	275.1	*
181 	N-(4-ethylphenyl)-N'-(4-isopropylphenyl)urea	1.39	283.2	*

Table II

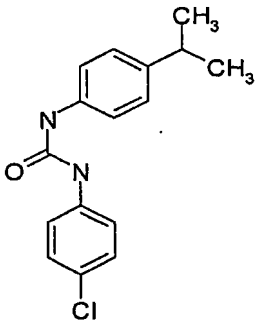
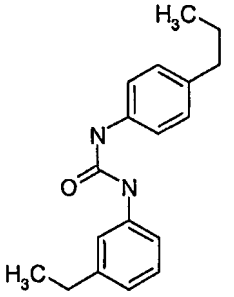
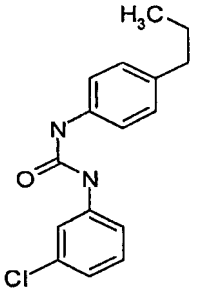
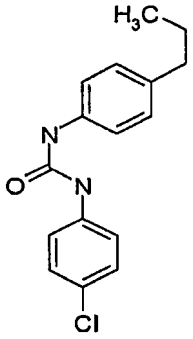
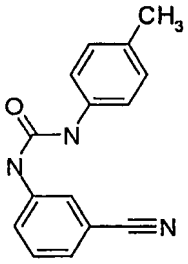
Compound	Name	R.T.	MS	IC_{50}
182 	N-(4-chlorophenyl)-N'-(4-isopropylphenyl)urea	1.39	289.1	*
183 	N-(3-ethylphenyl)-N'-(4-propylphenyl)urea	1.4	283.2	*
184 	N-(3-chlorophenyl)-N'-(4-propylphenyl)urea	1.39	289.1	*
185 	N-(4-chlorophenyl)-N'-(4-propylphenyl)urea	1.39	289.1	*
186 	N-(3-cyanophenyl)-N'-(4-methylphenyl)urea	1.27	252.1	*

Table II

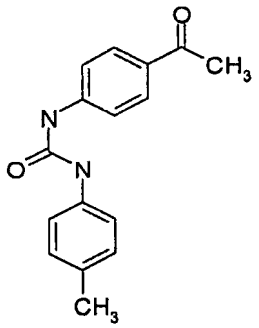
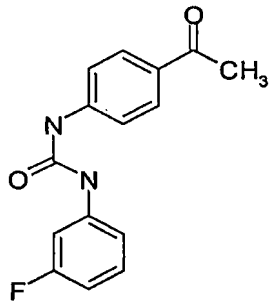
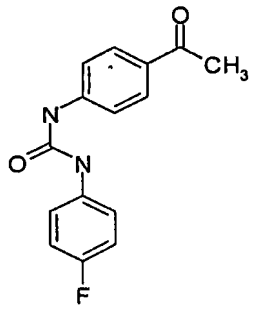
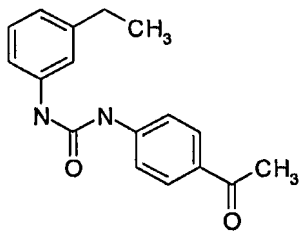
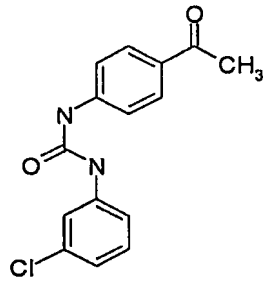
Compound	Name	R.T.	MS	IC_{50}
187 	N-(4-acetylphenyl)-N'-(4-methylphenyl)urea	1.27	269.1	*
188 	N-(4-acetylphenyl)-N'-(3-fluorophenyl)urea	1.27	273.1	*
189 	N-(4-acetylphenyl)-N'-(4-fluorophenyl)urea	1.24	273.1	*
190 	N-(4-acetylphenyl)-N'-(3-ethylphenyl)urea	1.3	283.1	*
191 	N-(4-acetylphenyl)-N'-(3-chlorophenyl)urea	1.3	289.1	*

Table II

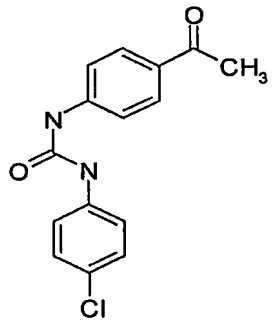
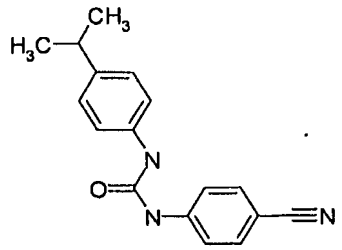
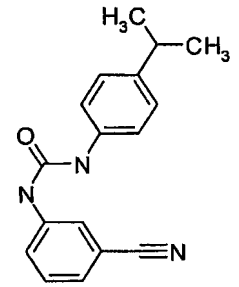
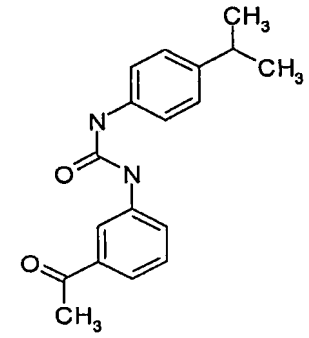
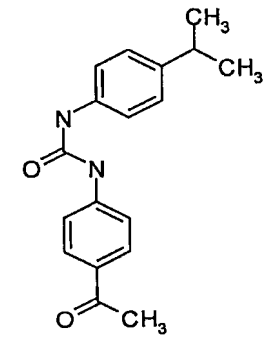
Compound	Name	R.T.	MS	IC_{50}
192 	N-(4-acetylphenyl)-N'-(4-chlorophenyl)urea	1.3	289.1	*
193 	N-(4-cyanophenyl)-N'-(4-isopropylphenyl)urea	1.34	280.2	*
194 	N-(3-cyanophenyl)-N'-(4-isopropylphenyl)urea	1.33	280.2	*
195 	N-(3-acetylphenyl)-N'-(4-isopropylphenyl)urea	1.33	297.2	*
196 	N-(4-acetylphenyl)-N'-(4-isopropylphenyl)urea	1.33	297.2	*

Table II

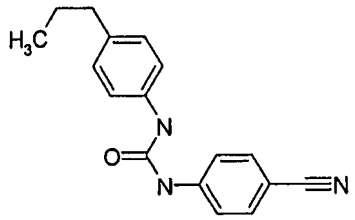
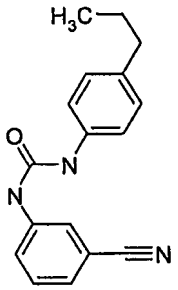
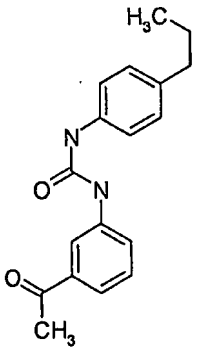
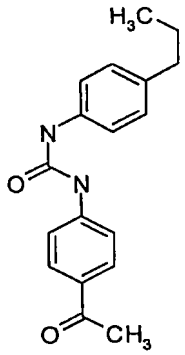
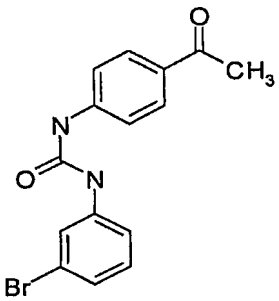
	Compound	Name	R.T.	MS	IC_{50}
197		N-(4-cyanophenyl)-N'-(4-propylphenyl)urea	1.35	280.2	*
198		N-(3-cyanophenyl)-N'-(4-propylphenyl)urea	1.34	280.2	*
199		N-(3-acetylphenyl)-N'-(4-propylphenyl)urea	1.34	297.2	*
200		N-(4-acetylphenyl)-N'-(4-propylphenyl)urea	1.34	297.2	*
201		N-(4-acetylphenyl)-N'-(3-bromophenyl)urea	1.31	333.0	*

Table II

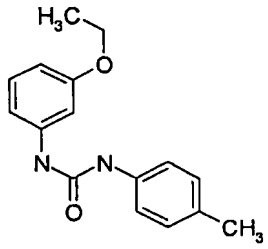
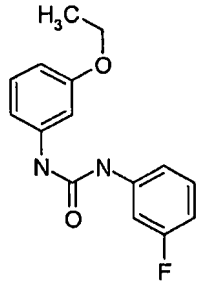
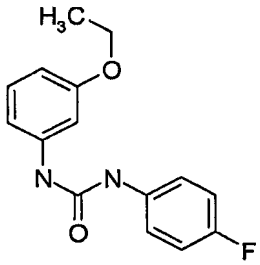
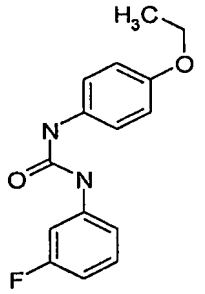
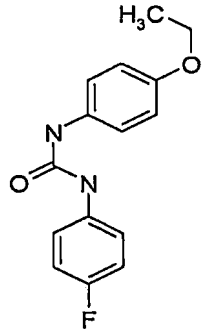
Compound	Name	R.T.	MS	IC_{50}
202 	N-(3-ethoxyphenyl)-N'-(4-methylphenyl)urea	1.31	271.1	*
203 	N-(3-ethoxyphenyl)-N'-(3-fluorophenyl)urea	1.3	275.1	*
204 	N-(3-ethoxyphenyl)-N'-(4-fluorophenyl)urea	1.29	275.1	*
205 	N-(4-ethoxyphenyl)-N'-(3-fluorophenyl)urea	1.29	275.1	*
206 	N-(4-ethoxyphenyl)-N'-(4-fluorophenyl)urea	1.27	275.1	*

Table II

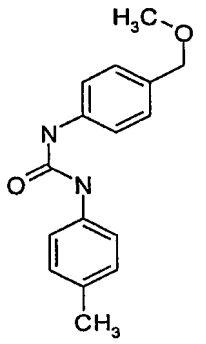
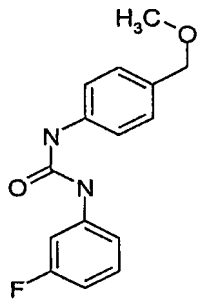
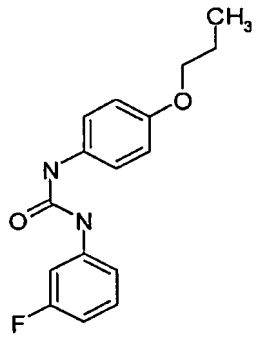
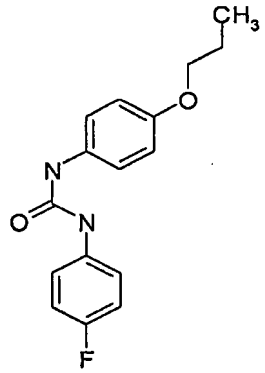
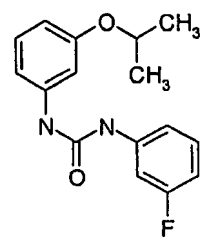
Compound	Name	R.T.	MS	IC_{50}
207 	N-[4-(methoxymethyl)phenyl]-N'-(4-methylphenyl)urea	1.27	271.1	*
208 	N-(3-fluorophenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.26	275.1	*
209 	N-(3-fluorophenyl)-N'-(4-propoxyphenyl)urea	1.33	289.1	*
210 	N-(4-fluorophenyl)-N'-(4-propoxyphenyl)urea	1.31	289.1	*
211 	N-(3-fluorophenyl)-N'-(3-isopropoxyphenyl)urea	1.33	289.1	*

Table II

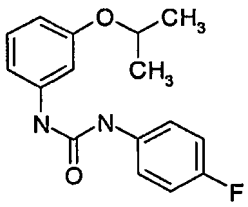
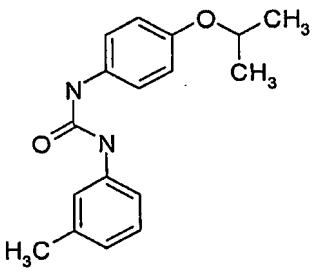
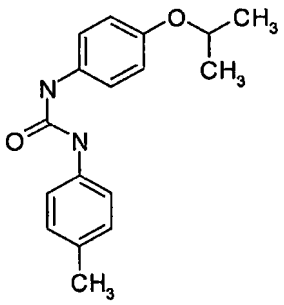
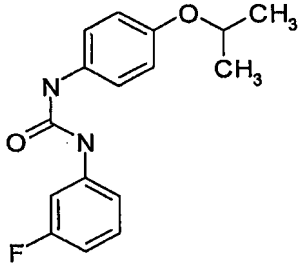
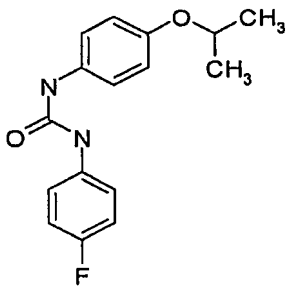
Compound	Name	R.T.	MS	IC_{50}
212 	N-(4-fluorophenyl)-N'-(3-isopropoxyphenyl)urea	1.31	289.1	*
213 	N-(4-isopropoxyphenyl)-N'-(3-methylphenyl)urea	1.32	285.2	*
214 	N-(4-isopropoxyphenyl)-N'-(4-methylphenyl)urea	1.32	285.1	*
215 	N-(3-fluorophenyl)-N'-(4-isopropoxyphenyl)urea	1.3	289.1	*
216 	N-(4-fluorophenyl)-N'-(4-isopropoxyphenyl)urea	1.29	289.1	*

Table II

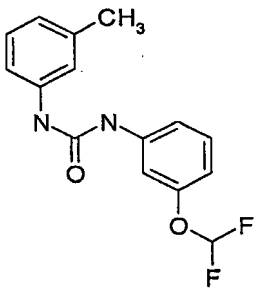
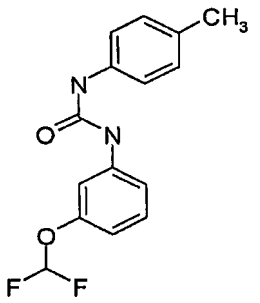
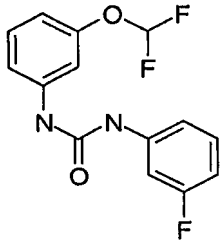
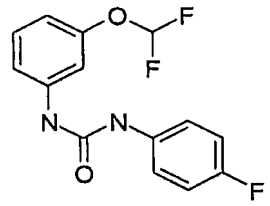
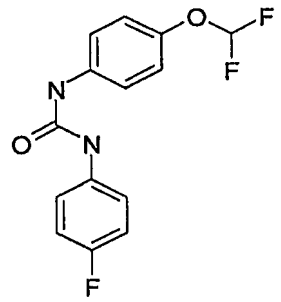
	Compound	Name	R.T.	MS	IC_{50}
217		N-[3-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea	1.3	293.1	*
218		N-[3-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea	1.3	293.1	*
219		N-[3-(difluoromethoxy)phenyl]-N'-(3-fluorophenyl)urea	1.29	297.1	*
220		N-[3-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea	1.28	297.1	*
221		N-[4-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea	1.27	297.1	*

Table II

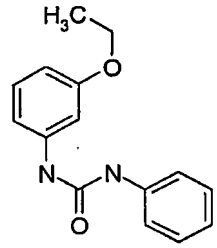
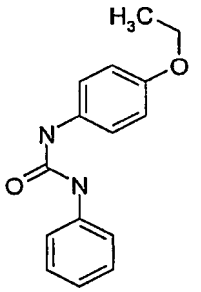
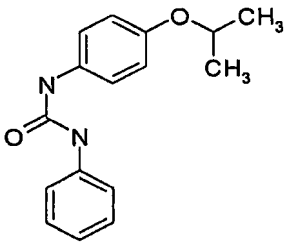
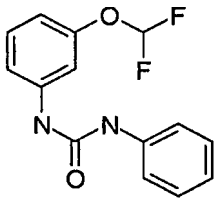
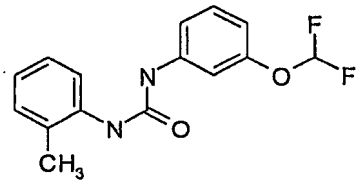
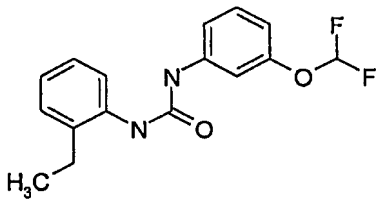
Compound	Name	R.T.	MS	IC_{50}
222 	N-(3-ethoxyphenyl)-N'-phenylurea	1.28	257.1	*
223 	N-(4-ethoxyphenyl)-N'-phenylurea	1.27	257.1	*
224 	N-(4-isopropoxyphenyl)-N'-phenylurea	1.29	271.1	*
225 	N-[3-(difluoromethoxy)phenyl]-N'-phenylurea	1.27	279.1	*
226 	N-[3-(difluoromethoxy)phenyl]-N'-(2-methylphenyl)urea	1.28	293.1	*
227 	N-[3-(difluoromethoxy)phenyl]-N'-(2-ethylphenyl)urea	1.31	307.1	*

Table II

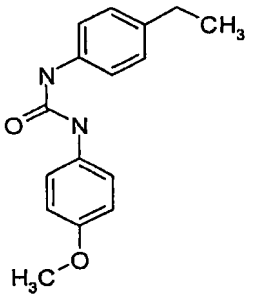
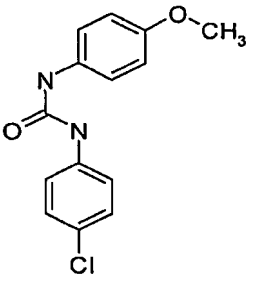
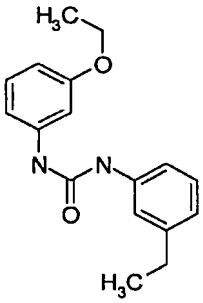
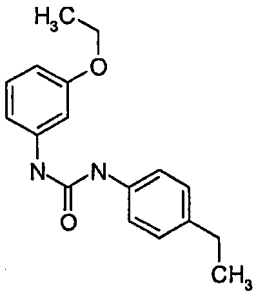
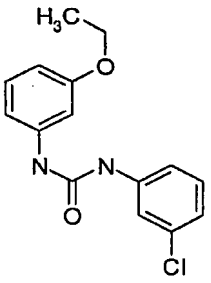
Compound	Name	R.T.	MS	IC_{50}
228 	N-(4-ethylphenyl)-N'-(4-methoxyphenyl)urea	1.22	271.2	*
229 	N-(4-chlorophenyl)-N'-(4-methoxyphenyl)urea	1.21	277.1	*
230 	N-(3-ethoxyphenyl)-N'-(3-ethylphenyl)urea	1.26	285.2	*
231 	N-(3-ethoxyphenyl)-N'-(4-ethylphenyl)urea	1.26	285.2	*
232 	N-(3-chlorophenyl)-N'-(3-ethoxyphenyl)urea	1.25	291.2	*

Table II

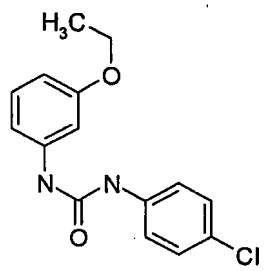
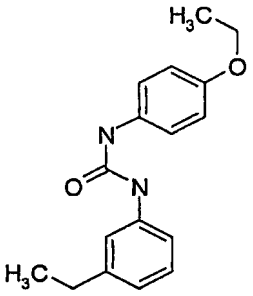
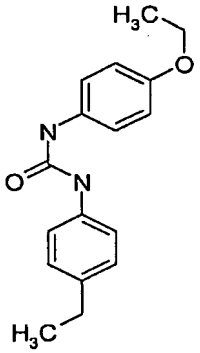
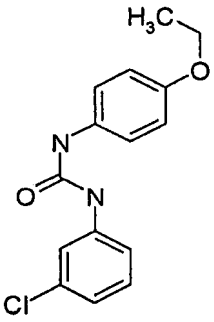
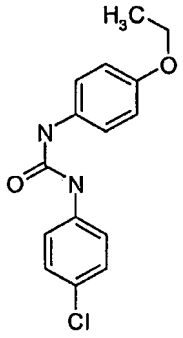
Compound	Name	R.T.	MS	IC_{50}
233 	N-(4-chlorophenyl)-N'-(3-ethoxyphenyl)urea	1.25	291.2	*
234 	N-(4-ethoxyphenyl)-N'-(3-ethylphenyl)urea	1.24	285.2	*
235 	N-(4-ethoxyphenyl)-N'-(4-ethylphenyl)urea	1.24	285.2	*
236 	N-(3-chlorophenyl)-N'-(4-ethoxyphenyl)urea	1.24	291.2	*
237 	N-(4-chlorophenyl)-N'-(4-ethoxyphenyl)urea	1.24	291.2	*

Table II

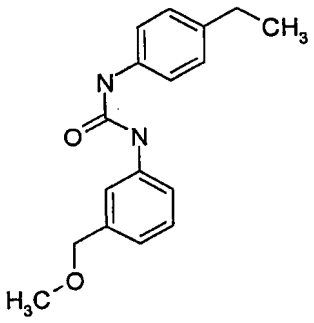
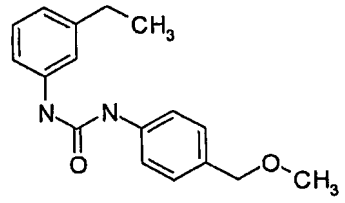
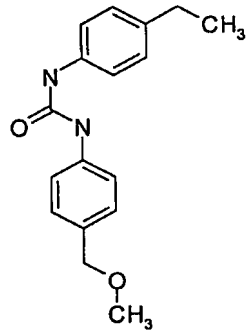
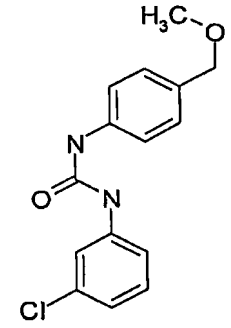
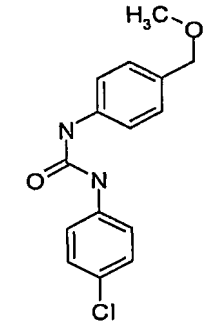
Compound	Name	R.T.	MS	IC_{50}
238 	N-(4-ethylphenyl)-N'-[3-(methoxymethyl)phenyl]urea	1.23	285.2	*
239 	N-(3-ethylphenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.23	285.2	*
240 	N-(4-ethylphenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.23	285.2	*
241 	N-(3-chlorophenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.22	291.1	*
242 	N-(4-chlorophenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.22	291.2	*

Table II

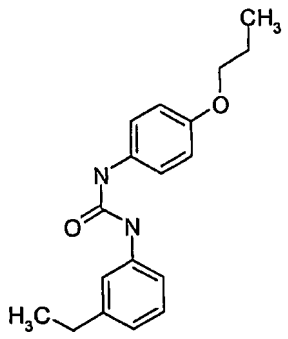
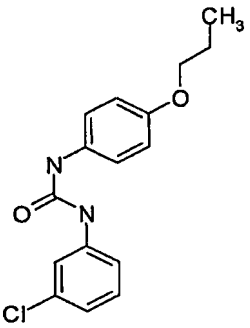
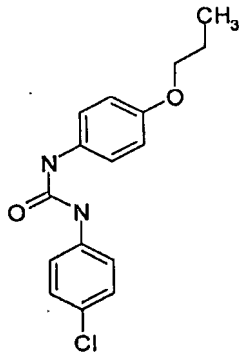
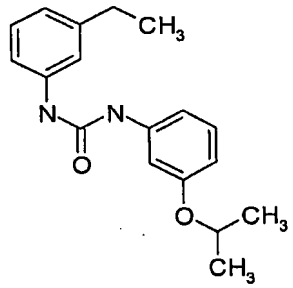
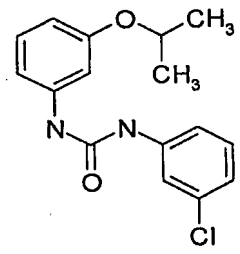
Compound	Name	R.T.	MS	IC_{50}
243 	N-(3-ethylphenyl)-N'-(4-propoxyphenyl)urea	1.28	299.2	*
244 	N-(3-chlorophenyl)-N'-(4-propoxyphenyl)urea	1.28	305.2	*
245 	N-(4-chlorophenyl)-N'-(4-propoxyphenyl)urea	1.27	305.2	*
246 	N-(3-ethylphenyl)-N'-(3-isopropoxyphenyl)urea	1.27	299.2	*
247 	N-(3-chlorophenyl)-N'-(3-isopropoxyphenyl)urea	1.27	305.2	*

Table II

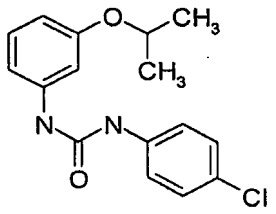
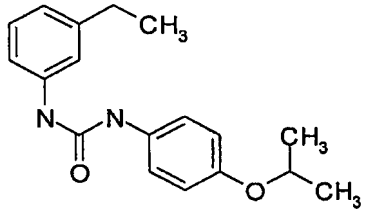
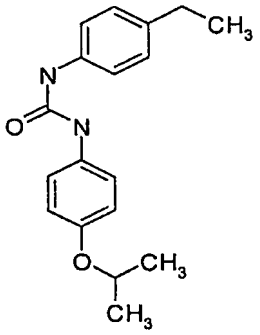
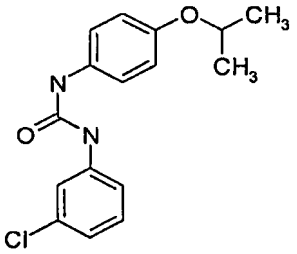
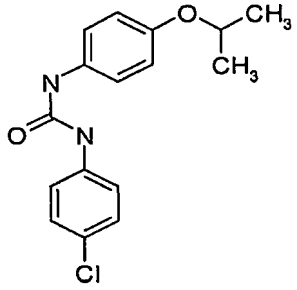
Compound	Name	R.T.	MS	IC_{50}
248 	N-(4-chlorophenyl)-N'-(3-isopropoxyphenyl)urea	1.27	305.2	*
249 	N-(3-ethylphenyl)-N'-(4-isopropoxyphenyl)urea	1.26	299.2	*
250 	N-(4-ethylphenyl)-N'-(4-isopropoxyphenyl)urea	1.26	299.2	*
251 	N-(3-chlorophenyl)-N'-(4-isopropoxyphenyl)urea	1.26	305.2	*
252 	N-(4-chlorophenyl)-N'-(4-isopropoxyphenyl)urea	1.26	305.2	*

Table II

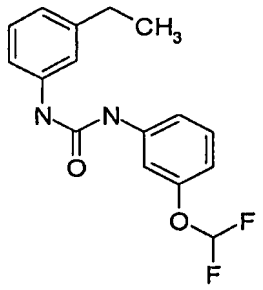
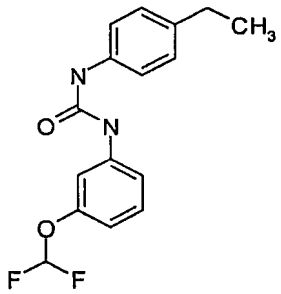
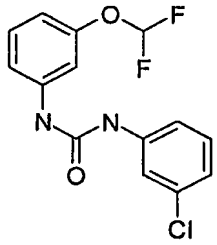
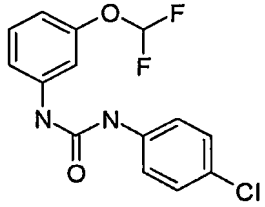
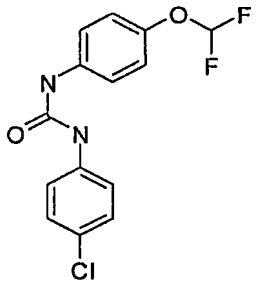
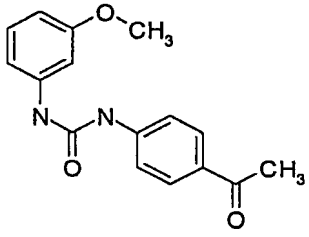
	Compound	Name	R.T.	MS	IC_{50}
253		N-[3-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea	1.25	307.2	*
254		N-[3-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea	1.25	307.2	*
255		N-(3-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.25	259.2	*
256		N-(4-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.25	313.1	*
257		N-(4-chlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.31	313.1	*
258		N-(4-acetylphenyl)-N'-(3-methoxyphenyl)urea	1.17	285.2	*

Table II

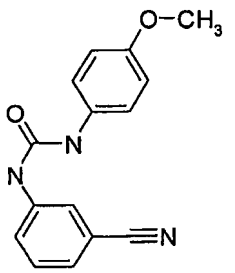
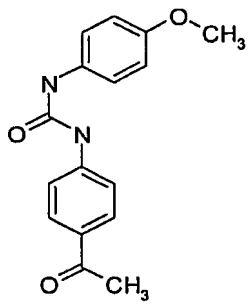
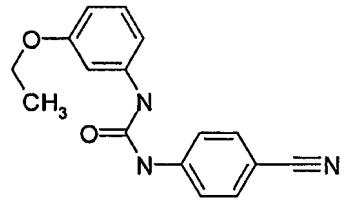
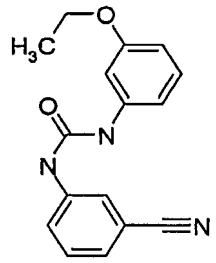
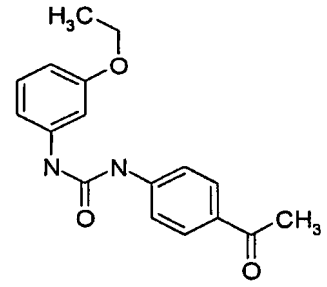
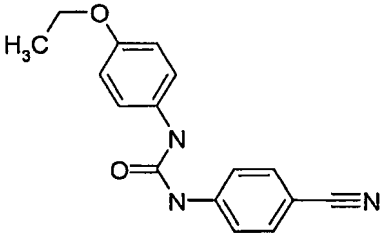
Compound	Name	R.T.	MS	IC_{50}
259 	N-(3-cyanophenyl)-N'-(4-methoxyphenyl)urea	1.15	268.2	*
260 	N-(4-acetylphenyl)-N'-(4-methoxyphenyl)urea	1.15	285.2	*
261 	N-(4-cyanophenyl)-N'-(3-ethoxyphenyl)urea	1.27	282.2	*
262 	N-(3-cyanophenyl)-N'-(3-ethoxyphenyl)urea	1.2	282.2	*
263 	N-(4-acetylphenyl)-N'-(3-ethoxyphenyl)urea	1.2	299.2	*
264 	N-(4-cyanophenyl)-N'-(4-ethoxyphenyl)urea	1.26	282.1	*

Table II

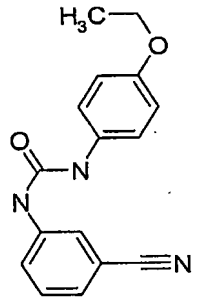
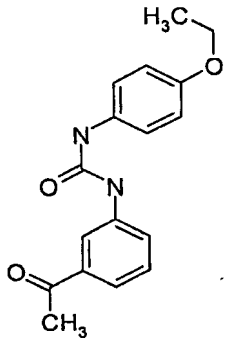
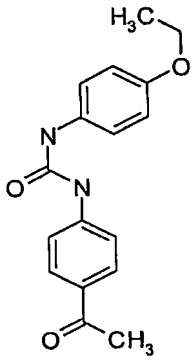
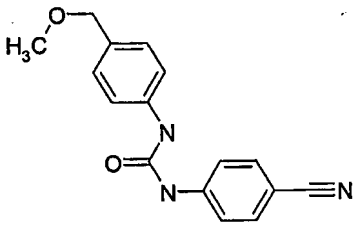
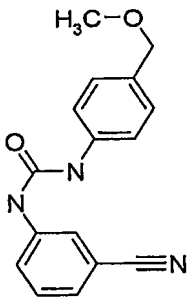
Compound	Name	R.T.	MS	IC_{50}
265 	N-(3-cyanophenyl)-N'-(4-ethoxyphenyl)urea	1.18	282.2	*
266 	N-(3-acetylphenyl)-N'-(4-ethoxyphenyl)urea	1.18	299.2	*
267 	N-(4-acetylphenyl)-N'-(4-ethoxyphenyl)urea	1.18	299.2	*
268 	N-(4-cyanophenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.24	282.1	*
269 	N-(3-cyanophenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.15	282.2	*

Table II

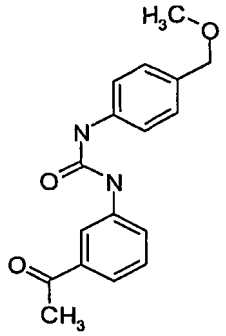
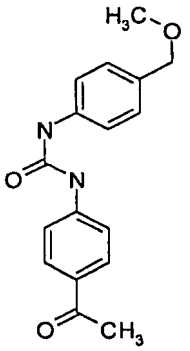
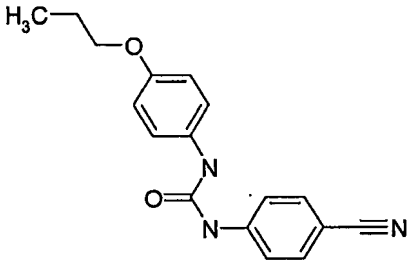
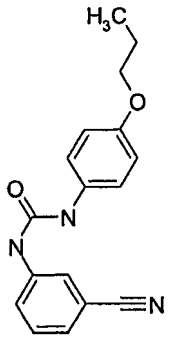
Compound	Name	R.T.	MS	IC_{50}
270 	N-(3-acetylphenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.15	299.2	*
271 	N-(4-acetylphenyl)-N'-[4-(methoxymethyl)phenyl]urea	1.15	299.2	*
272 	N-(4-cyanophenyl)-N'-(4-propoxyphenyl)urea	1.31	296.2	*
273 	N-(3-cyanophenyl)-N'-(4-propoxyphenyl)urea	1.23	296.2	*

Table II

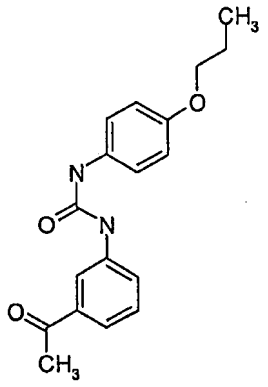
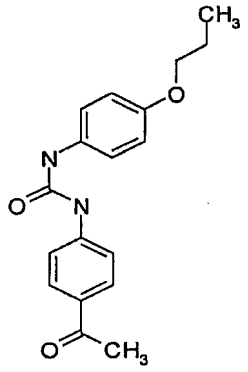
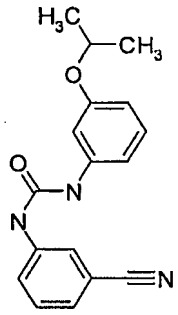
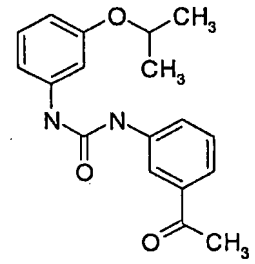
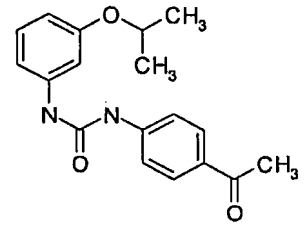
Compound	Name	R.T.	MS	IC_{50}
274 	N-(3-acetylphenyl)-N'-(4-propoxyphenyl)urea	1.22	625.4	*
275 	N-(4-acetylphenyl)-N'-(4-propoxyphenyl)urea	1.22	313.2	*
276 	N-(3-cyanophenyl)-N'-(3-isopropoxyphenyl)urea	1.22	591.4	*
277 	N-(3-acetylphenyl)-N'-(3-isopropoxyphenyl)urea	1.21	313.2	*
278 	N-(4-acetylphenyl)-N'-(3-isopropoxyphenyl)urea	1.22	313.2	*

Table II

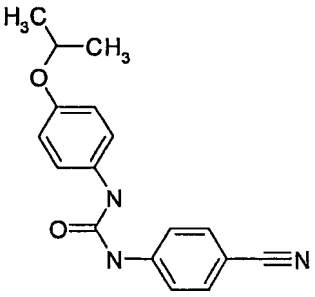
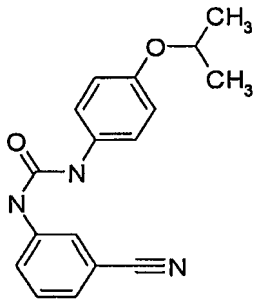
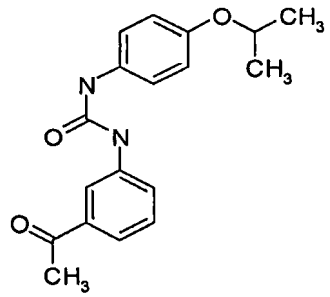
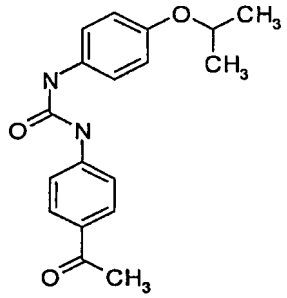
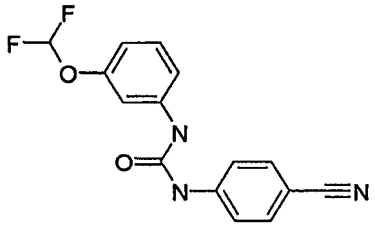
	Compound	Name	R.T.	MS	IC_{50}
279		N-(4-cyanophenyl)-N'-(4-isopropoxyphenyl)urea	1.28	296.2	*
280		N-(3-cyanophenyl)-N'-(4-isopropoxyphenyl)urea	1.2	296.2	*
281		N-(3-acetylphenyl)-N'-(4-isopropoxyphenyl)urea	1.2	313.2	*
282		N-(4-acetylphenyl)-N'-(4-isopropoxyphenyl)urea	1.2	313.2	*
283		N-(4-cyanophenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.26	304.1	*

Table II

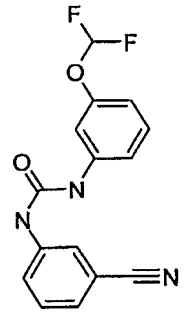
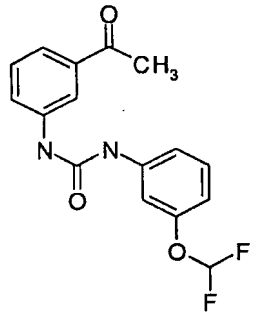
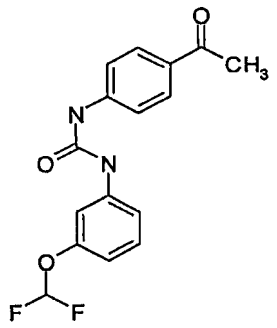
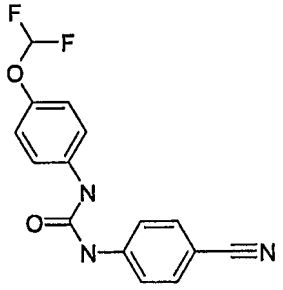
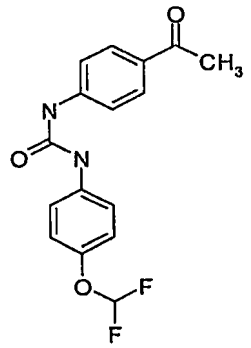
	Compound	Name	R.T.	MS	IC_{50}
284		N-(3-cyanophenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.27	304.1	*
285		N-(3-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.19	321.2	*
286		N-(4-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea	1.19	321.2	*
287		N-(4-cyanophenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.26	304.1	*
288		N-(4-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea	1.19	237.1	*

Table 3

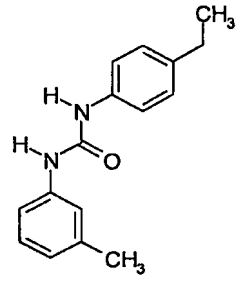
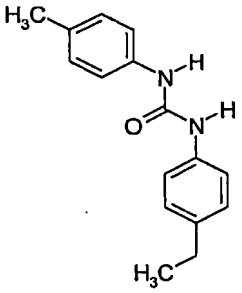
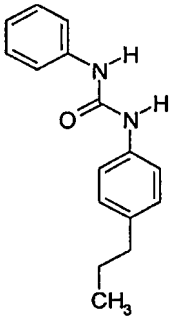
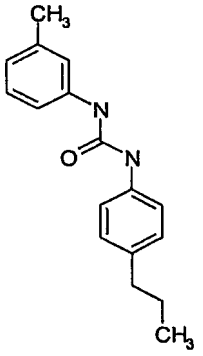
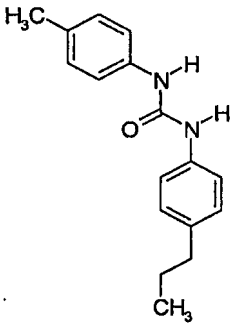
Compound	Name	R.T.	MS	IC50
289 	N-(4-ethylphenyl)-N'-(3-methylphenyl)urea	1.3	255.2	*
290 	N-(4-ethylphenyl)-N'-(4-methylphenyl)urea	1.3	255.21	*
291 	N-phenyl-N'-(4-propylphenyl)urea	1.3	255.19	*
292 	1-(3-methylphenyl)-3-(4-propylphenyl)urea	1.33	269.22	*
293 	N-(4-methylphenyl)-N'-(4-propylphenyl)urea	1.33	269.23	*

Table 3

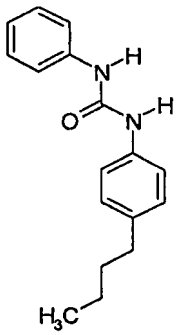
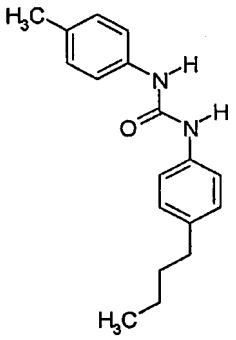
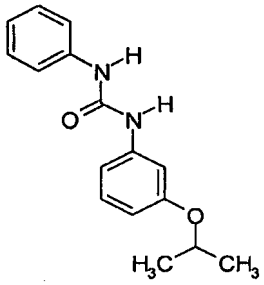
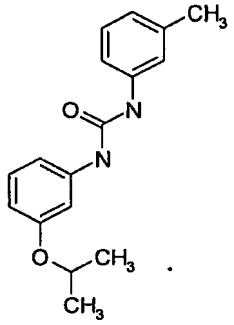
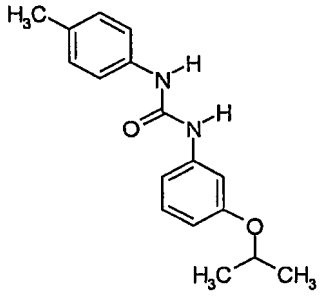
Compound	Name	R.T.	MS	IC50
294 	N-(4-butylphenyl)-N'-phenylurea	1.34	269.22	*
295 	N-(4-butylphenyl)-N'-(4-methylphenyl)urea	1.37	283.25	*
296 	N-(3-isopropoxyphenyl)-N'-phenylurea	1.26	271.19	
297 	1-(3-isopropoxyphenyl)-3-(3-methylphenyl)urea	1.29	285.21	*
298 	N-(3-isopropoxyphenyl)-N'-(4-methylphenyl)urea	1.29	285.21	*

Table 3

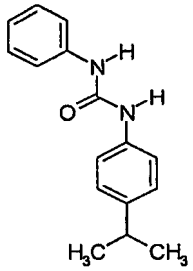
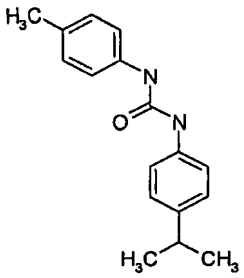
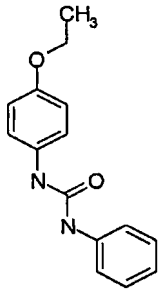
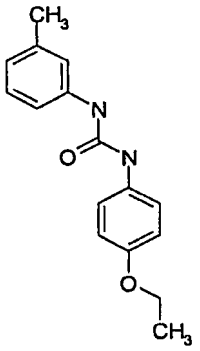
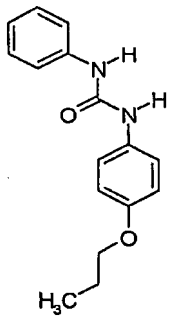
Compound	Name	R.T.	MS	IC50
299 	N-(4-isopropylphenyl)-N'-phenylurea	1.3	255.2	
300 	1-(4-isopropylphenyl)-3-(4-methylphenyl)urea	1.32	269.22	*
301 	N-(4-ethoxyphenyl)-N'-phenylurea	1.22	257.19	
302 	1-(4-ethoxyphenyl)-3-(3-methylphenyl)urea	1.26	271.2	*
303 	N-phenyl-N'-(4-propoxyphenyl)urea	1.27	271.2	*

Table 3

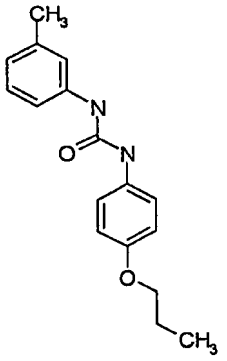
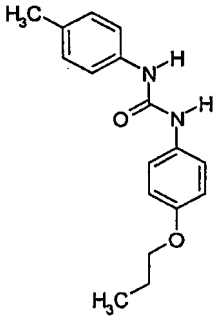
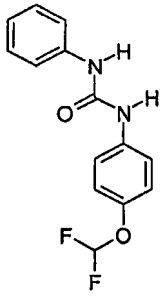
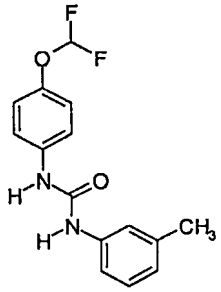
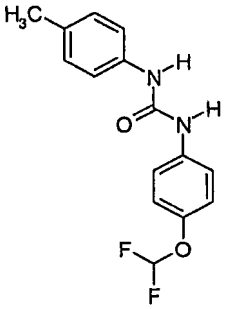
Compound	Name	R.T.	MS	IC50
304 	1-(3-methylphenyl)-3-(4-propoxyphenyl)urea	1.3	285.21	*
305 	N-(4-methylphenyl)-N'-(4-propoxyphenyl)urea	1.29	285.22	
306 	N-[4-(difluoromethoxy)phenyl]-N'-phenylurea	1.23	279.15	*
307 	N-[4-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea	1.26	293.17	*
308 	N-[4-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea	1.26	293.19	*

Table 3

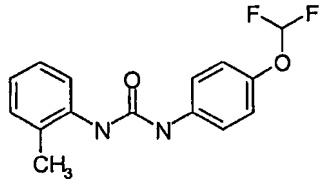
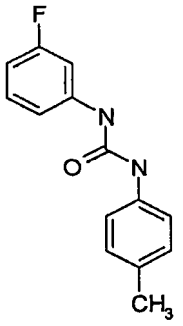
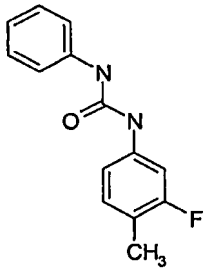
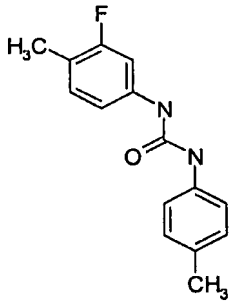
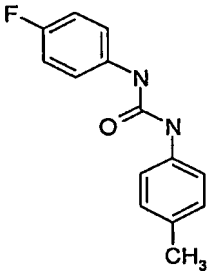
Compound	Name	R.T.	MS	IC50
309 	1-[4-(difluoromethoxy)phenyl]-3-(2-methylphenyl)urea	1.23	293.17	
310 	1-(3-fluorophenyl)-3-(4-methylphenyl)urea	1.26	245.16	
311 	1-(3-fluoro-4-methylphenyl)-3-phenylurea	1.26	245.16	
312 	1-(3-fluoro-4-methylphenyl)-3-(4-methylphenyl)urea	1.29	259.19	*
313 	1-(4-fluorophenyl)-3-(4-methylphenyl)urea	1.24	245.16	

Table 3

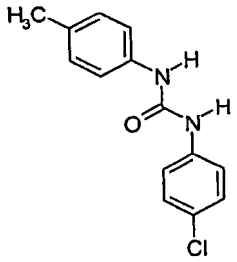
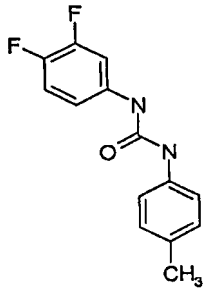
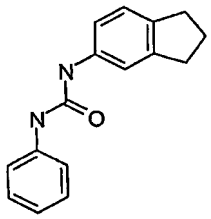
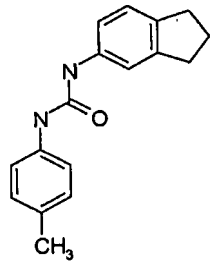
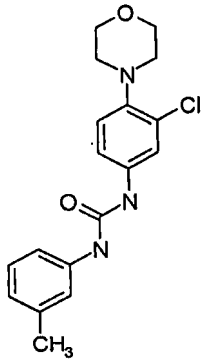
Compound	Name	R.T.	MS	IC50
314 	N-(4-chlorophenyl)-N'-(4-methylphenyl)urea	1.29	261.16	*
315 	1-(3,4-difluorophenyl)-3-(4-methylphenyl)urea	1.28	263.16	
316 	1-(2,3-dihydro-1H-inden-5-yl)-3-phenylurea	1.28	253.18	*
317 	1-(2,3-dihydro-1H-inden-5-yl)-3-(4-methylphenyl)urea	1.31	267.2	
318 	1-(3-chloro-4-morpholin-4-ylphenyl)-3-(3-methylphenyl)urea	1.23	346.2	*

Table 3

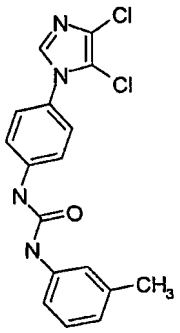
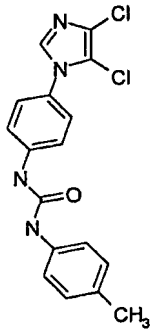
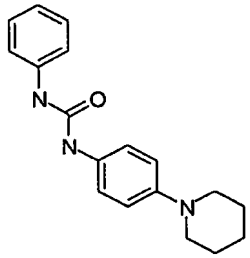
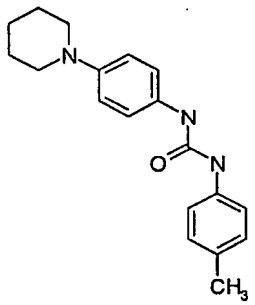
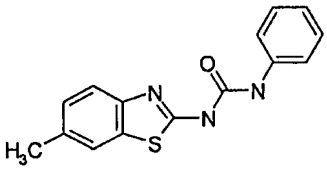
Compound	Name	R.T.	MS	IC50
319 	1-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-3-(3-methylphenyl)urea	1.26	361.13	*
320 	1-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-3-(4-methylphenyl)urea	1.25	361.13	*
321 	1-phenyl-3-(4-piperidin-1-ylphenyl)urea	1.05	296.23	*
322 	1-(4-methylphenyl)-3-(4-piperidin-1-ylphenyl)urea	1.08	310.25	*
323 	1-(6-methyl-1,3-benzothiazol-2-yl)-3-phenylurea	1.37	284.14	*

Table 3

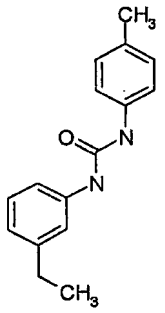
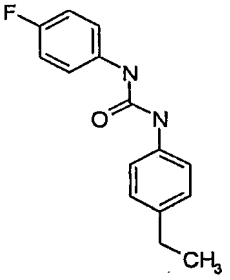
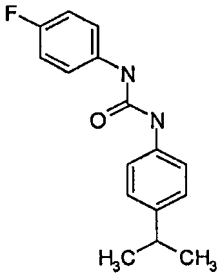
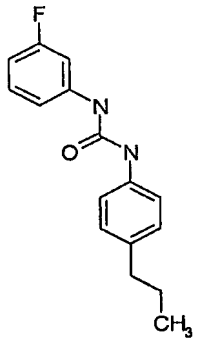
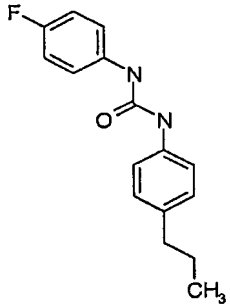
Compound	Name	R.T.	MS	IC50
324 	1-(3-ethylphenyl)-3-(4-methylphenyl)urea	1.25	255.19	*
325 	1-(4-ethylphenyl)-3-(4-fluorophenyl)urea	1.24	259.17	*
326 	1-(4-fluorophenyl)-3-(4-isopropylphenyl)urea	1.26	273.19	*
327 	1-(3-fluorophenyl)-3-(4-propylphenyl)urea	1.28	273.19	*
328 	1-(4-fluorophenyl)-3-(4-propylphenyl)urea	1.28	273.19	*

Table 3

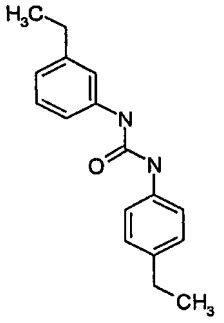
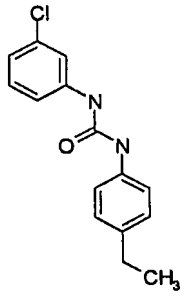
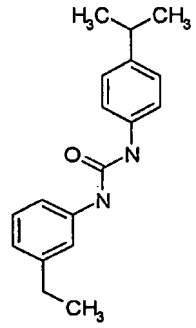
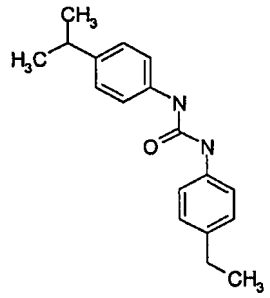
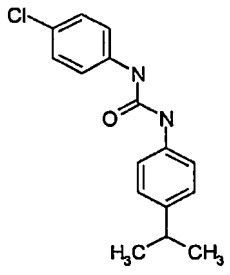
Compound	Name	R.T.	MS	IC50
329 	1-(3-ethylphenyl)-3-(4-ethylphenyl)urea	1.37	269.16	*
330 	1-(3-chlorophenyl)-3-(4-ethylphenyl)urea	1.35	275.1	*
331 	1-(3-ethylphenyl)-3-(4-isopropylphenyl)urea	1.39	283.18	
332 	1-(4-ethylphenyl)-3-(4-isopropylphenyl)urea	1.39	283.18	*
333 	1-(4-chlorophenyl)-3-(4-isopropylphenyl)urea	1.39	289.13	*

Table 3

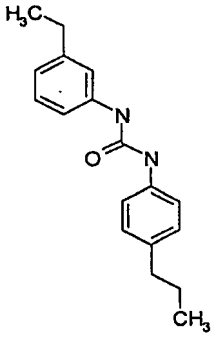
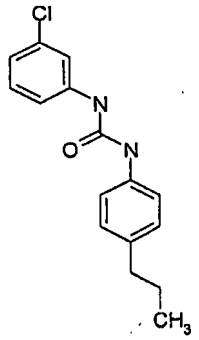
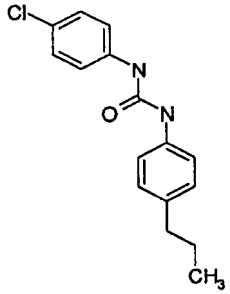
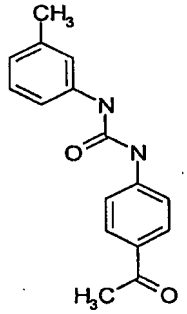
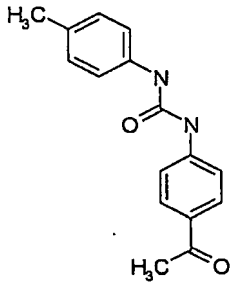
Compound	Name	R.T.	MS	IC50
334 	1-(3-ethylphenyl)-3-(4-propylphenyl)urea	1.4	283.18	*
335 	1-(3-chlorophenyl)-3-(4-propylphenyl)urea	1.39	289.12	*
336 	1-(4-chlorophenyl)-3-(4-propylphenyl)urea	1.39	289.13	*
337 	1-(4-acetylphenyl)-3-(3-methylphenyl)urea	1.27	269.14	
338 	1-(4-acetylphenyl)-3-(4-methylphenyl)urea	1.27	269.14	*

Table 3

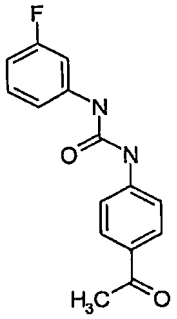
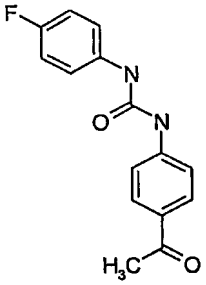
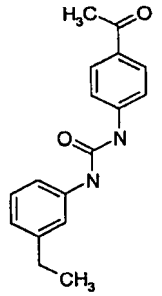
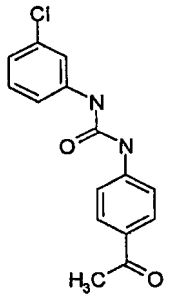
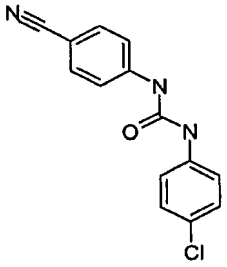
Compound	Name	R.T.	MS	IC50
339 	1-(4-acetylphenyl)-3-(3-fluorophenyl)urea	1.27	273.13	*
340 	1-(4-acetylphenyl)-3-(4-fluorophenyl)urea	1.24	273.12	*
341 	1-(4-acetylphenyl)-3-(3-ethylphenyl)urea	1.3	283.15	*
342 	1-(4-acetylphenyl)-3-(3-chlorophenyl)urea	1.3	289.09	*
343 	1-(4-chlorophenyl)-3-(4-cyanophenyl)urea	1.32	272.07	

Table 3

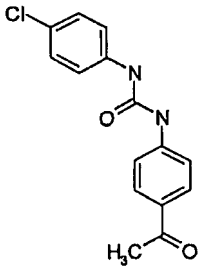
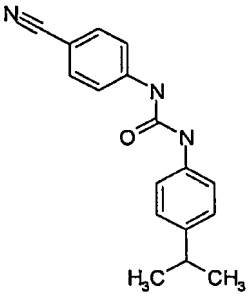
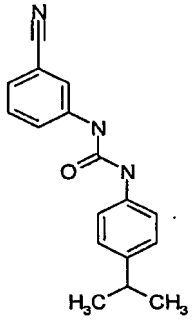
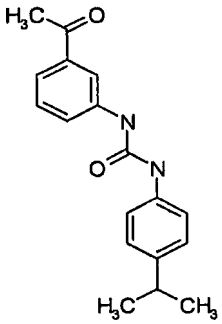
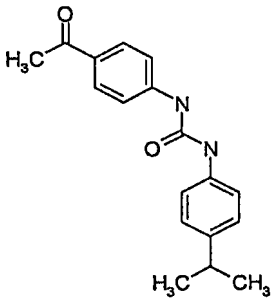
Compound	Name	R.T.	MS	IC50
344 	1-(4-acetylphenyl)-3-(4-chlorophenyl)urea	1.3	289.1	*
345 	1-(4-cyanophenyl)-3-(4-isopropylphenyl)urea	1.34	280.16	*
346 	1-(3-cyanophenyl)-3-(4-isopropylphenyl)urea	1.33	280.15	*
347 	1-(3-acetylphenyl)-3-(4-isopropylphenyl)urea	1.33	297.16	*
348 	1-(4-acetylphenyl)-3-(4-isopropylphenyl)urea	1.33	297.17	*

Table 3

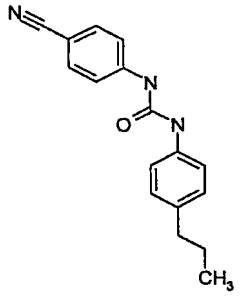
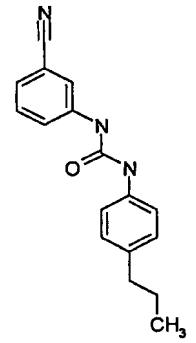
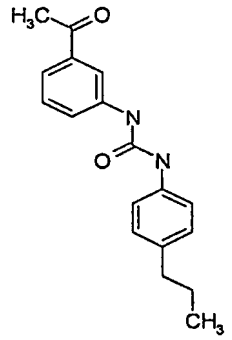
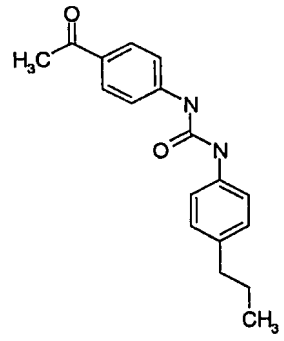
Compound	Name	R.T.	MS	IC50
349 	1-(4-cyanophenyl)-3-(4-propylphenyl)urea	1.35	280.17	*
350 	1-(3-cyanophenyl)-3-(4-propylphenyl)urea	1.34	280.15	*
351 	1-(3-acetylphenyl)-3-(4-propylphenyl)urea	1.34	297.17	*
352 	1-(4-acetylphenyl)-3-(4-propylphenyl)urea	1.34	297.18	*

Table 3

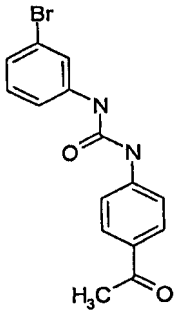
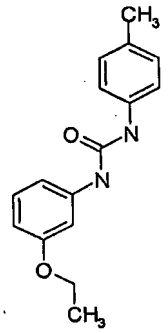
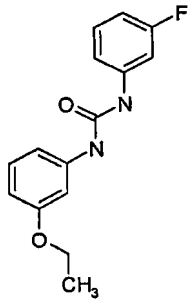
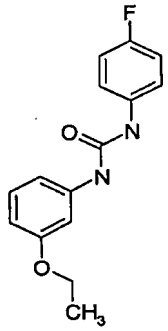
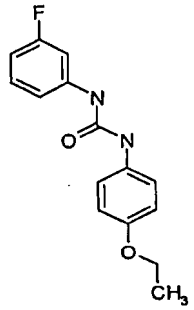
Compound	Name	R.T.	MS	IC50
353 	1-(4-acetylphenyl)-3-(3-bromophenyl)urea	1.31	333.05	*
354 	1-(3-ethoxyphenyl)-3-(4-methylphenyl)urea	1.31	271.14	*
355 	1-(3-ethoxyphenyl)-3-(3-fluorophenyl)urea	1.3	275.13	*
356 	1-(3-ethoxyphenyl)-3-(4-fluorophenyl)urea	1.29	275.13	*
357 	1-(4-ethoxyphenyl)-3-(3-fluorophenyl)urea	1.29	275.13	*

Table 3

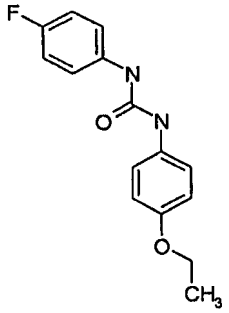
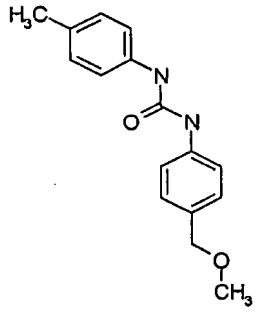
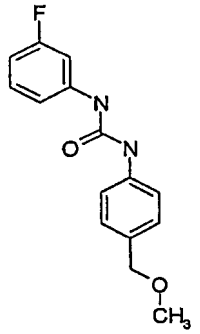
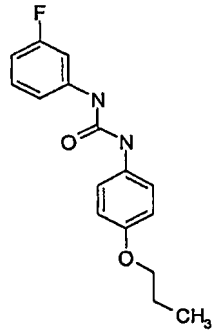
Compound	Name	R.T.	MS	IC50
358 	1-(4-ethoxyphenyl)-3-(4-fluorophenyl)urea	1.27	275.13	*
359 	1-[4-(methoxymethyl)phenyl]-3-(4-methylphenyl)urea	1.27	271.14	*
360 	1-(3-fluorophenyl)-3-[4-(methoxymethyl)phenyl]urea	1.26	275.12	*
361 	1-(3-fluorophenyl)-3-(4-propoxyphenyl)urea	1.33	289.13	*

Table 3

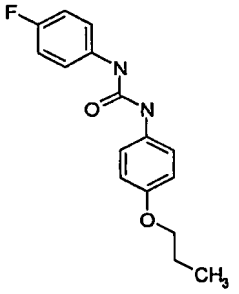
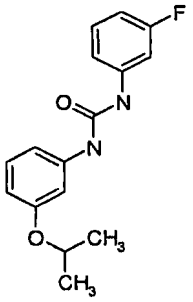
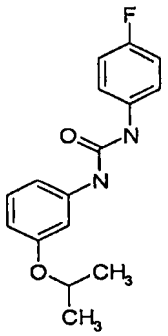
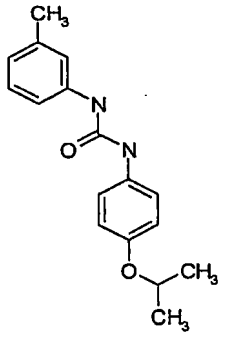
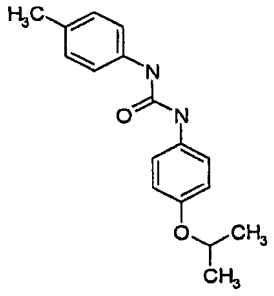
Compound	Name	R.T.	MS	IC50
362 	1-(4-fluorophenyl)-3-(4-propoxyphenyl)urea	1.31	289.14	*
363 	1-(3-fluorophenyl)-3-(3-isopropoxyphenyl)urea	1.33	289.13	*
364 	1-(4-fluorophenyl)-3-(3-isopropoxyphenyl)urea	1.31	289.13	*
365 	1-(4-isopropoxyphenyl)-3-(3-methylphenyl)urea	1.32	285.15	*
366 	1-(4-isopropoxyphenyl)-3-(4-methylphenyl)urea	1.32	285.15	*

Table 3

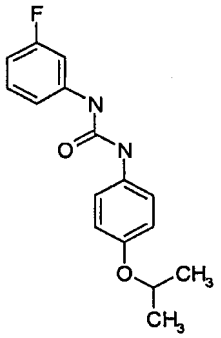
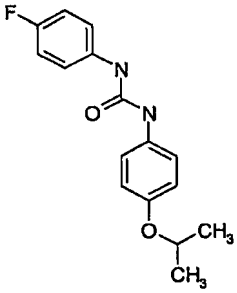
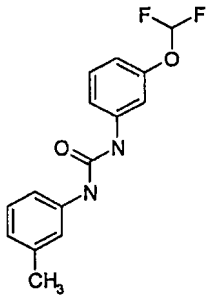
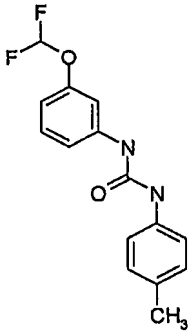
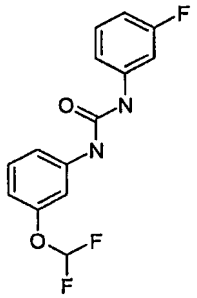
Compound	Name	R.T.	MS	IC50
367 	1-(3-fluorophenyl)-3-(4-isopropoxyphenyl)urea	1.3	289.13	*
368 	1-(4-fluorophenyl)-3-(4-isopropoxyphenyl)urea	1.29	289.13	*
369 	1-[3-(difluoromethoxy)phenyl]-3-(3-methylphenyl)urea	1.3	293.11	*
370 	1-[3-(difluoromethoxy)phenyl]-3-(4-methylphenyl)urea	1.3	293.11	*
371 	1-[3-(difluoromethoxy)phenyl]-3-(3-fluorophenyl)urea	1.29	297.09	*

Table 3

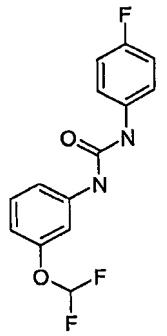
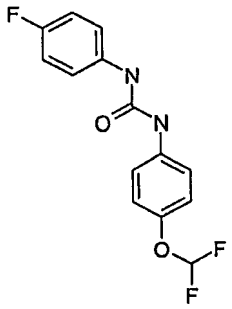
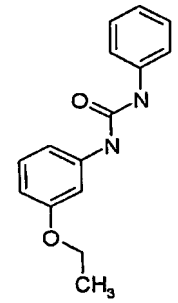
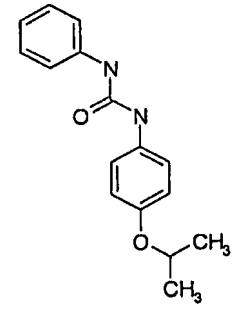
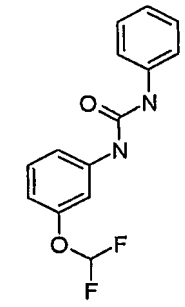
Compound	Name	R.T.	MS	IC50
372 	1-[3-(difluoromethoxy)phenyl]-3-(4-fluorophenyl)urea	1.28	297.09	*
373 	1-[4-(difluoromethoxy)phenyl]-3-(4-fluorophenyl)urea	1.27	297.1	*
374 	1-(3-ethoxyphenyl)-3-phenylurea	1.28	257.12	*
375 	1-(4-isopropoxyphenyl)-3-phenylurea	1.29	271.13	*
376 	1-[3-(difluoromethoxy)phenyl]-3-phenylurea	1.27	279.09	*

Table 3

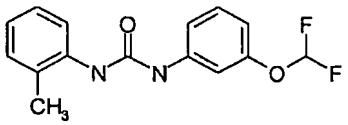
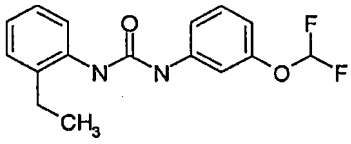
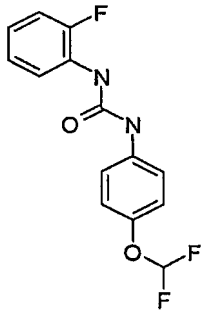
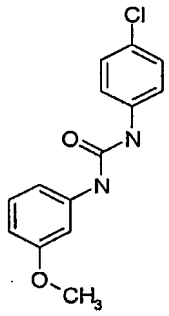
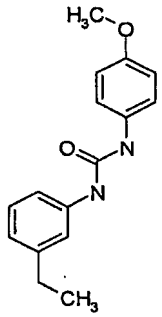
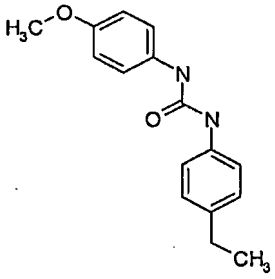
Compound	Name	R.T.	MS	IC50
377 	1-[3-(difluoromethoxy)phenyl]-3-(2-methylphenyl)urea	1.28	293.1	*
378 	1-[3-(difluoromethoxy)phenyl]-3-(2-ethylphenyl)urea	1.31	307.11	*
379 	1-[4-(difluoromethoxy)phenyl]-3-(2-fluorophenyl)urea	1.28	297.08	
380 	1-(4-chlorophenyl)-3-(3-methoxyphenyl)urea	1.22	277.13	
381 	1-(3-ethylphenyl)-3-(4-methoxyphenyl)urea	1.21	271.19	
382 	1-(4-ethylphenyl)-3-(4-methoxyphenyl)urea	1.22	271.2	*

Table 3

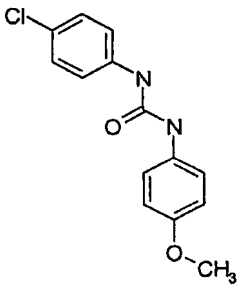
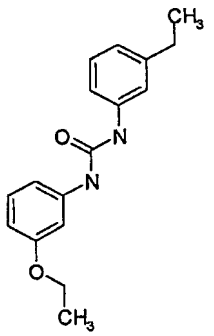
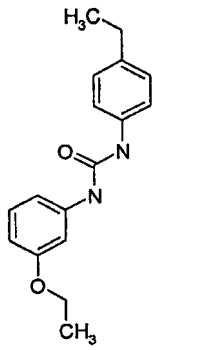
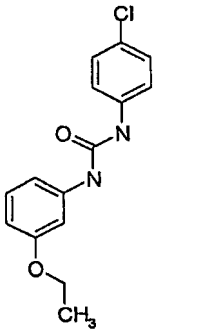
Compound	Name	R.T.	MS	IC50
383 	1-(4-chlorophenyl)-3-(4-methoxyphenyl)urea	1.21	277.13	*
384 	1-(3-ethoxyphenyl)-3-(3-ethylphenyl)urea	1.26	285.21	*
385 	1-(3-ethoxyphenyl)-3-(4-ethylphenyl)urea	1.26	285.22	*
386 	1-(4-chlorophenyl)-3-(3-ethoxyphenyl)urea	1.25	291.15	*

Table 3

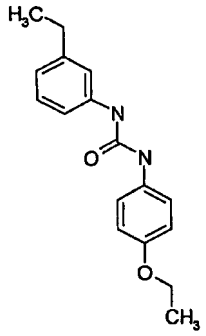
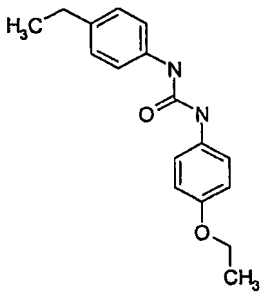
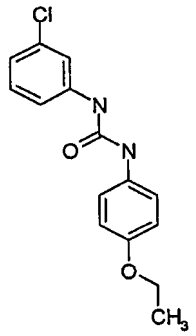
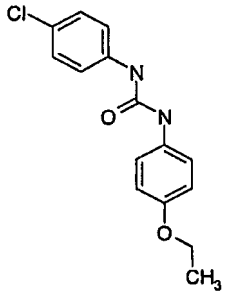
Compound	Name	R.T.	MS	IC50
387 	1-(4-ethoxyphenyl)-3-(3-ethylphenyl)urea	1.24	285.21	*
388 	1-(4-ethoxyphenyl)-3-(4-ethylphenyl)urea	1.24	285.22	*
389 	1-(3-chlorophenyl)-3-(4-ethoxyphenyl)urea	1.24	291.15	*
390 	1-(4-chlorophenyl)-3-(4-ethoxyphenyl)urea	1.24	291.16	*

Table 3

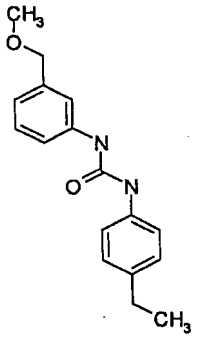
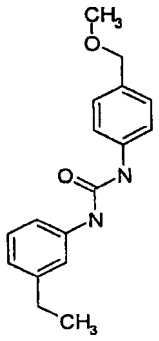
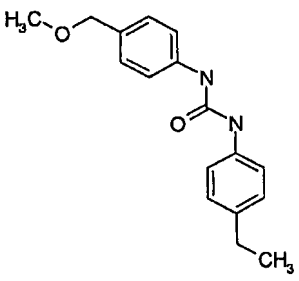
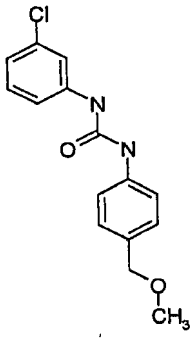
Compound	Name	R.T.	MS	IC50
391 	1-(4-ethylphenyl)-3-[3-(methoxymethyl)phenyl]urea	1.23	285.22	*
392 	1-(3-ethylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.23	285.22	*
393 	1-(4-ethylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.23	285.22	*
394 	1-(3-chlorophenyl)-3-[4-(methoxymethyl)phenyl]urea	1.22	291.15	*

Table 3

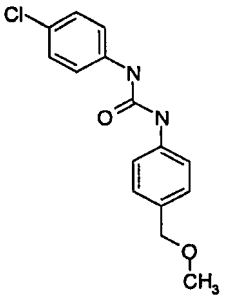
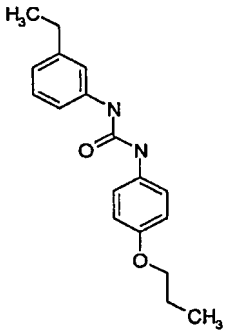
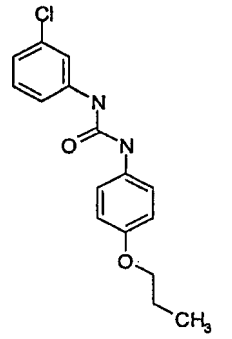
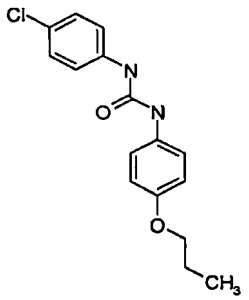
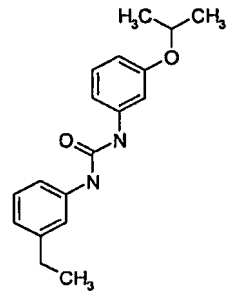
Compound	Name	R.T.	MS	IC50
395 	1-(4-chlorophenyl)-3-[4-(methoxymethyl)phenyl]urea	1.22	291.15	*
396 	1-(3-ethylphenyl)-3-(4-propoxyphenyl)urea	1.28	299.24	*
397 	1-(3-chlorophenyl)-3-(4-propoxyphenyl)urea	1.28	305.17	*
398 	1-(4-chlorophenyl)-3-(4-propoxyphenyl)urea	1.27	305.17	*
399 	1-(3-ethylphenyl)-3-(3-isopropoxyphenyl)urea	1.27	299.23	*

Table 3

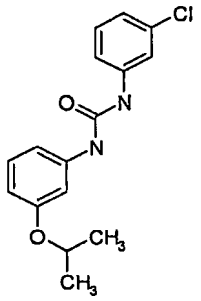
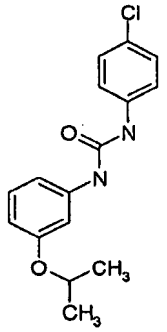
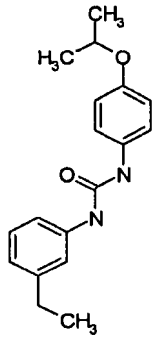
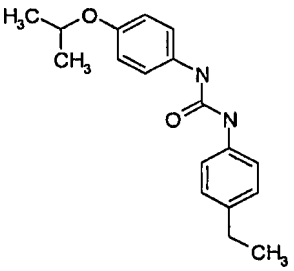
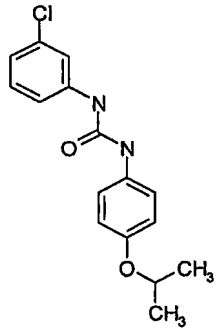
Compound	Name	R.T.	MS	IC50
400 	1-(3-chlorophenyl)-3-(3-isopropoxyphenyl)urea	1.27	305.17	*
401 	1-(4-chlorophenyl)-3-(3-isopropoxyphenyl)urea	1.27	305.17	*
402 	1-(3-ethylphenyl)-3-(4-isopropoxyphenyl)urea	1.26	299.24	*
403 	1-(4-ethylphenyl)-3-(4-isopropoxyphenyl)urea	1.26	299.24	*
404 	1-(3-chlorophenyl)-3-(4-isopropoxyphenyl)urea	1.26	305.18	*

Table 3

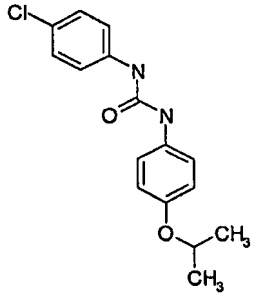
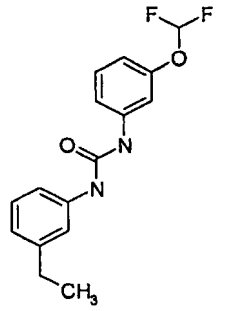
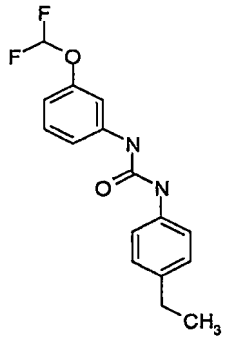
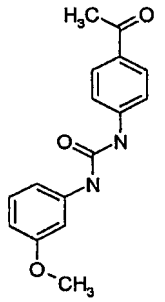
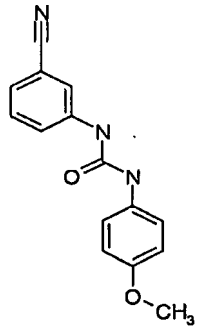
Compound	Name	R.T.	MS	IC50
405 	1-(4-chlorophenyl)-3-(4-isopropoxyphenyl)urea	1.26	305.17	*
406 	1-[3-(difluoromethoxy)phenyl]-3-(3-ethylphenyl)urea	1.25	307.19	*
407 	1-[3-(difluoromethoxy)phenyl]-3-(4-ethylphenyl)urea	1.25	307.18	*
408 	1-(4-acetylphenyl)-3-(3-methoxyphenyl)urea	1.17	285.19	*
409 	1-(3-cyanophenyl)-3-(4-methoxyphenyl)urea	1.15	268.16	*

Table 3

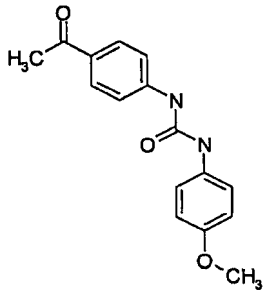
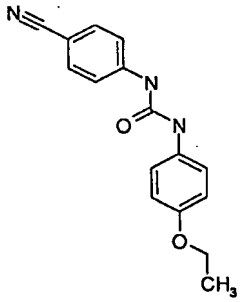
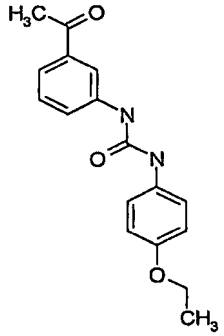
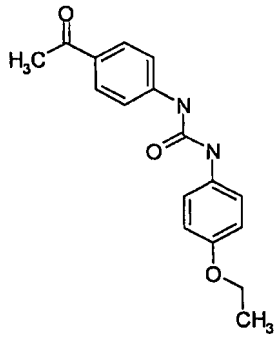
Compound	Name	R.T.	MS	IC50
410 	1-(4-acetylphenyl)-3-(4-methoxyphenyl)urea	1.15	285.19	*
411 	1-(4-cyanophenyl)-3-(4-ethoxyphenyl)urea	1.26	282.15	*
412 	1-(3-acetylphenyl)-3-(4-ethoxyphenyl)urea	1.18	299.2	*
413 	1-(4-acetylphenyl)-3-(4-ethoxyphenyl)urea	1.18	299.2	*

Table 3

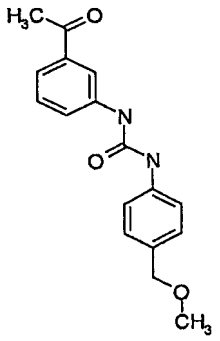
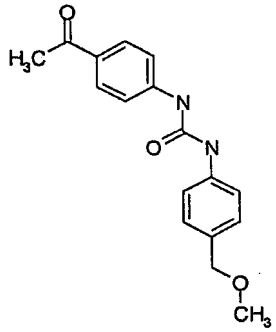
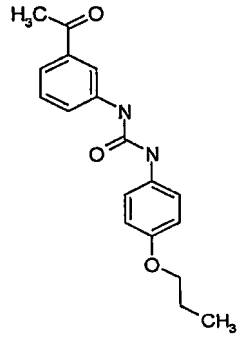
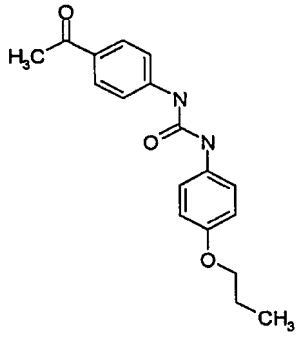
Compound	Name	R.T.	MS	IC50
414 	1-(3-acetylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.15	299.2	*
415 	1-(4-acetylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.15	299.2	*
416 	1-(3-acetylphenyl)-3-(4-propoxyphenyl)urea			*
417 	1-(4-acetylphenyl)-3-(4-propoxyphenyl)urea	1.22	313.23	*

Table 3

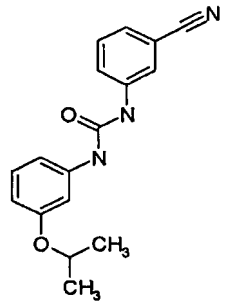
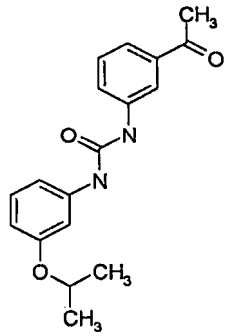
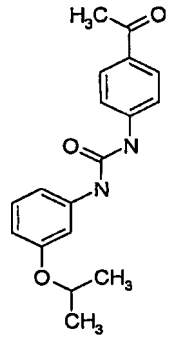
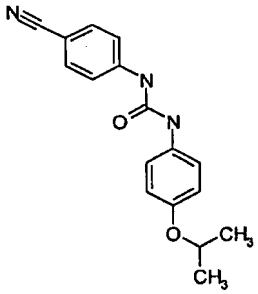
Compound	Name	R.T.	MS	IC50
418 	1-(3-cyanophenyl)-3-(3-isopropoxyphenyl)urea			*
419 	1-(3-acetylphenyl)-3-(3-isopropoxyphenyl)urea	1.21	313.22	*
420 	1-(4-acetylphenyl)-3-(3-isopropoxyphenyl)urea	1.22	313.22	*
421 	1-(4-cyanophenyl)-3-(4-isopropoxyphenyl)urea	1.28	296.16	*

Table 3

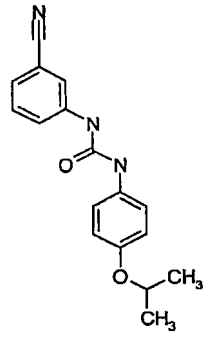
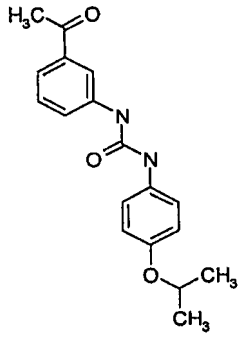
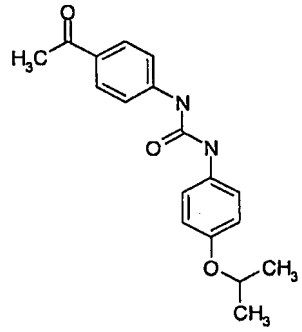
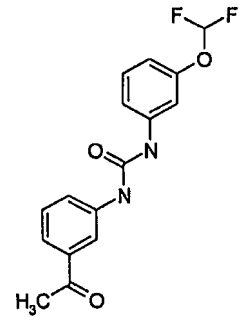
Compound	Name	R.T.	MS	IC50
422 	1-(3-cyanophenyl)-3-(4-isopropoxyphenyl)urea	1.2	296.2	*
423 	1-(3-acetylphenyl)-3-(4-isopropoxyphenyl)urea	1.2	313.22	*
424 	1-(4-acetylphenyl)-3-(4-isopropoxyphenyl)urea	1.2	313.22	*
425 	1-(3-acetylphenyl)-3-[3-(difluoromethoxy)phenyl]urea	1.19	321.18	*

Table 3

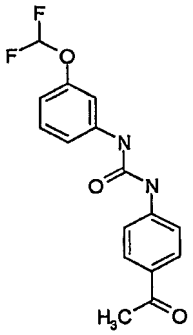
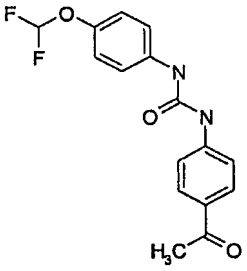
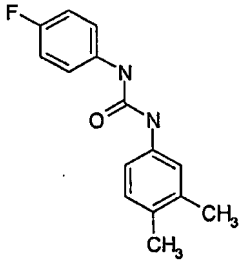
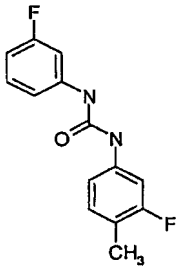
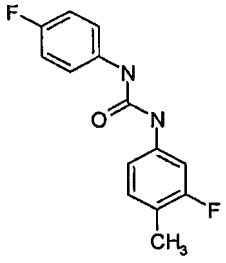
Compound	Name	R.T.	MS	IC50
426 	1-(4-acetylphenyl)-3-[3-(difluoromethoxy)phenyl]urea	1.19	321.21	*
427 	1-(4-acetylphenyl)-3-[4-(difluoromethoxy)phenyl]urea			*
428 	1-(3,4-dimethylphenyl)-3-(4-fluorophenyl)urea	1.3	259.13	*
429 	1-(3-fluoro-4-methylphenyl)-3-(3-fluorophenyl)urea	1.32	263.12	*
430 	1-(3-fluoro-4-methylphenyl)-3-(4-fluorophenyl)urea	1.31	263.12	*

Table 3

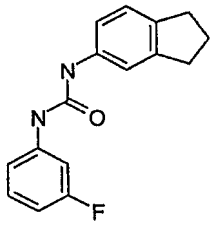
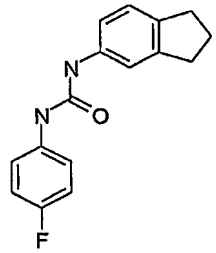
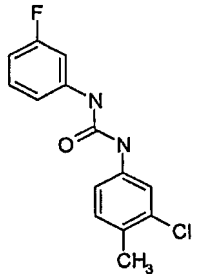
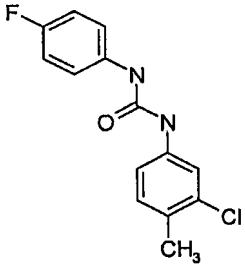
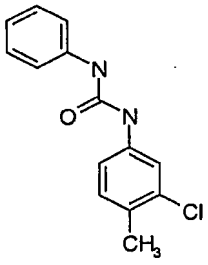
Compound	Name	R.T.	MS	IC50
431 	1-(2,3-dihydro-1H-inden-5-yl)-3-(3-fluorophenyl)urea	1.34	271.13	*
432 	1-(2,3-dihydro-1H-inden-5-yl)-3-(4-fluorophenyl)urea	1.33	271.13	*
433 	1-(3-chloro-4-methylphenyl)-3-(3-fluorophenyl)urea	1.35	279.08	*
434 	1-(3-chloro-4-methylphenyl)-3-(4-fluorophenyl)urea	1.34	279.09	*
435 	1-(3-chloro-4-methylphenyl)-3-phenylurea	1.34	261.08	*

Table 3

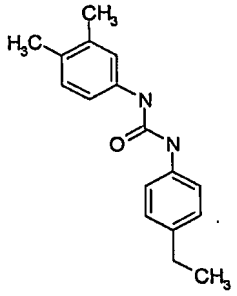
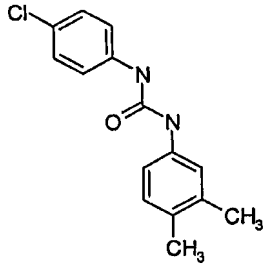
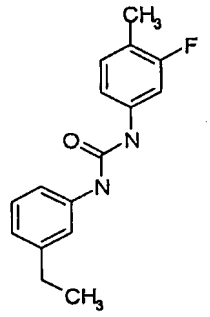
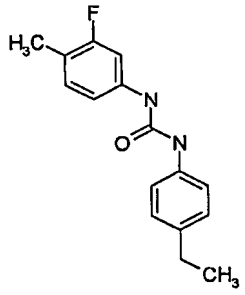
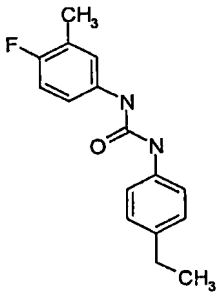
Compound	Name	R.T.	MS	IC50
436 	1-(3,4-dimethylphenyl)-3-(4-ethylphenyl)urea	1.36	269.18	*
437 	1-(4-chlorophenyl)-3-(3,4-dimethylphenyl)urea	1.36	275.13	*
438 	1-(3-ethylphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.36	273.16	*
439 	1-(4-ethylphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.35	273.17	*
440 	1-(4-ethylphenyl)-3-(4-fluoro-3-methylphenyl)urea	1.35	273.16	*

Table 3

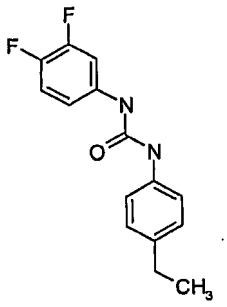
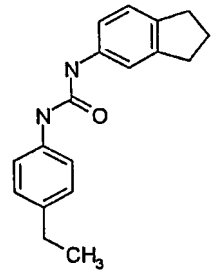
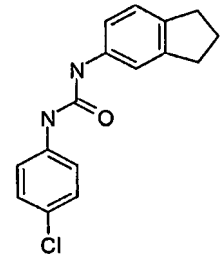
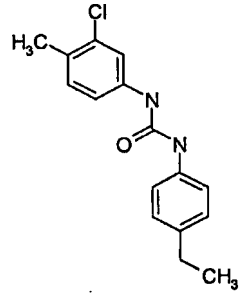
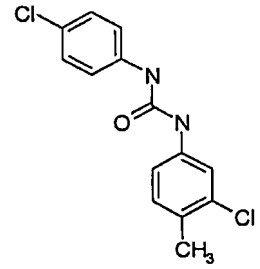
Compound	Name	R.T.	MS	IC50
441 	1-(3,4-difluorophenyl)-3-(4-ethylphenyl)urea	1.33	277.14	*
442 	1-(2,3-dihydro-1H-inden-5-yl)-3-(4-ethylphenyl)urea	1.38	281.18	*
443 	1-(4-chlorophenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea	1.37	287.13	*
444 	1-(3-chloro-4-methylphenyl)-3-(4-ethylphenyl)urea	1.39	289.14	*
445 	1-(3-chloro-4-methylphenyl)-3-(4-chlorophenyl)urea	1.38	295.1	*

Table 3

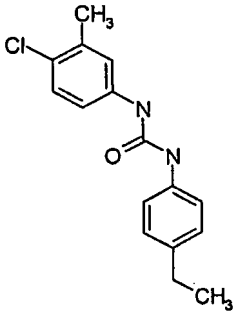
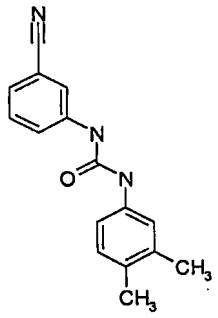
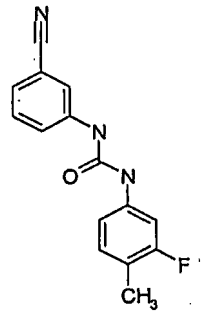
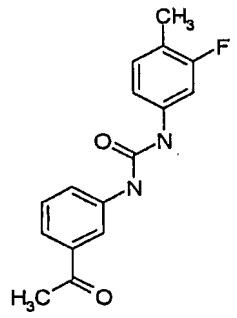
Compound	Name	R.T.	MS	IC50
446 	1-(4-chloro-3-methylphenyl)-3-(4-ethylphenyl)urea	1.39	289.15	*
447 	1-(3-cyanophenyl)-3-(3,4-dimethylphenyl)urea	1.3	266.14	*
448 	1-(3-cyanophenyl)-3-(3-fluoro-4-methylphenyl)urea	1.3	270.13	*
449 	1-(3-acetylphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.29	287.14	*

Table 3

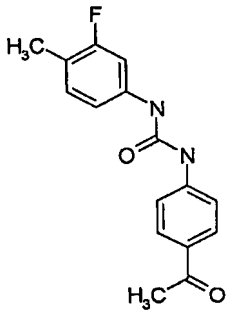
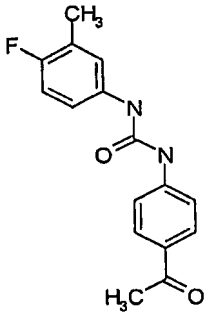
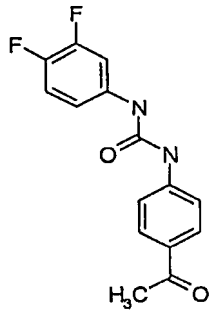
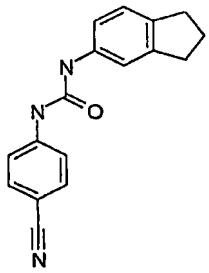
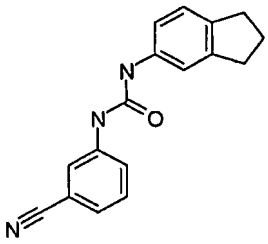
Compound	Name	R.T.	MS	IC50
450 	1-(4-acetylphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.29	287.14	*
451 	1-(4-acetylphenyl)-3-(4-fluoro-3-methylphenyl)urea	1.28	287.14	*
452 	1-(4-acetylphenyl)-3-(3,4-difluorophenyl)urea	1.28	291.12	*
453 	1-(4-cyanophenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea			*
454 	1-(3-cyanophenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea	1.32	278.14	*

Table 3

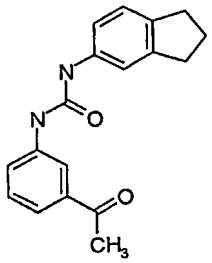
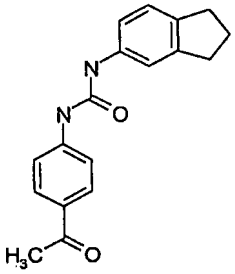
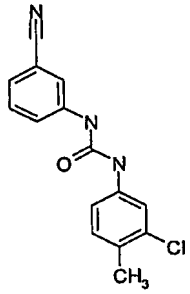
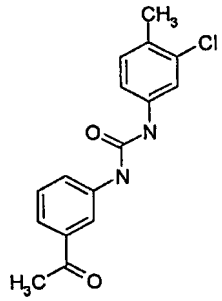
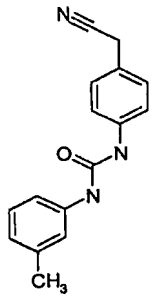
Compound	Name	R.T.	MS	IC50
455 	1-(3-acetylphenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea	1.31	295.15	*
456 	1-(4-acetylphenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea	1.31	295.16	*
457 	1-(3-chloro-4-methylphenyl)-3-(3-cyanophenyl)urea	1.34	286.1	*
458 	1-(3-acetylphenyl)-3-(3-chloro-4-methylphenyl)urea	1.33	303.11	*
459 	1-[4-(cyanomethyl)phenyl]-3-(3-methylphenyl)urea	1.24	266.17	*

Table 3

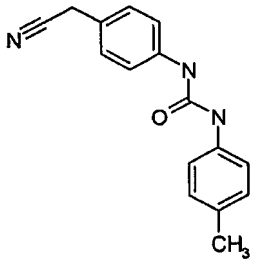
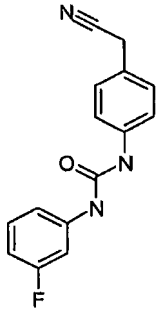
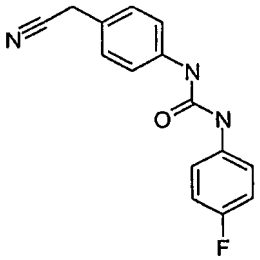
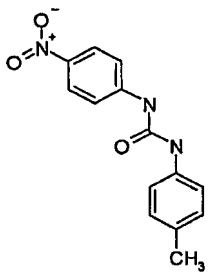
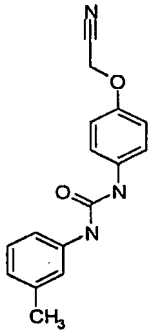
Compound	Name	R.T.	MS	IC50
460 	1-[4-(cyanomethyl)phenyl]-3-(4-methylphenyl)urea	1.24	266.18	*
461 	1-[4-(cyanomethyl)phenyl]-3-(3-fluorophenyl)urea	1.23	270.15	*
462 	1-[4-(cyanomethyl)phenyl]-3-(4-fluorophenyl)urea	1.22	270.15	*
463 	1-(4-methylphenyl)-3-(4-nitrophenyl)urea			*
464 	1-[4-(cyanomethoxy)phenyl]-3-(3-methylphenyl)urea	1.24	282.16	*

Table 3

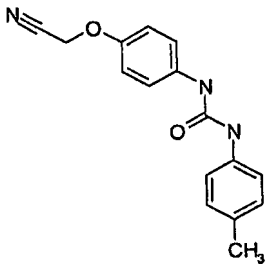
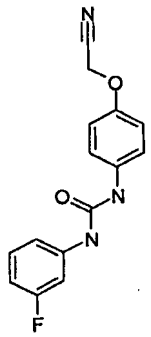
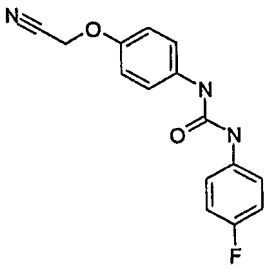
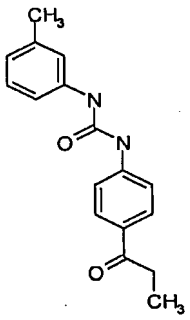
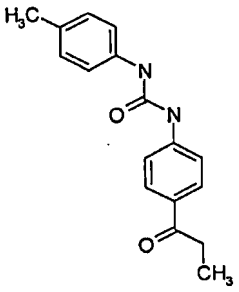
Compound	Name	R.T.	MS	IC50
465 	1-[4-(cyanomethoxy)phenyl]-3-(4-methylphenyl)urea	1.24	282.16	*
466 	1-[4-(cyanomethoxy)phenyl]-3-(3-fluorophenyl)urea	1.23	286.14	*
467 	1-[4-(cyanomethoxy)phenyl]-3-(4-fluorophenyl)urea	1.21	286.14	*
468 	1-(3-methylphenyl)-3-(4-propionylphenyl)urea	1.31	283.17	*
469 	1-(4-methylphenyl)-3-(4-propionylphenyl)urea	1.31	283.17	*

Table 3

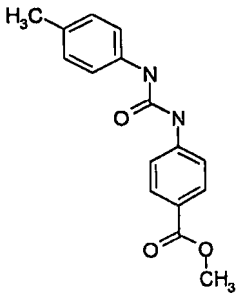
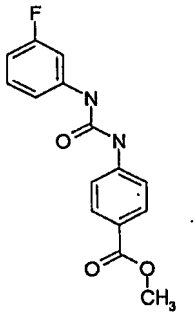
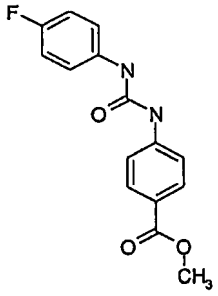
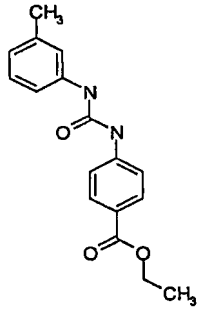
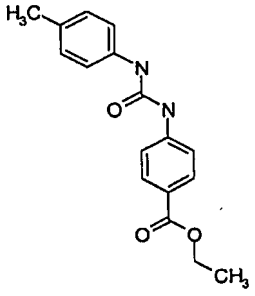
Compound	Name	R.T.	MS	IC50
470 	methyl 4-({[(4-methylphenyl)amino]carbonyl} amino)benzoate	1.3	285.16	*
471 	methyl 4-({[(3-fluorophenyl)amino]carbonyl} amino)benzoate	1.29	289.13	*
472 	methyl 4-({[(4-fluorophenyl)amino]carbonyl} amino)benzoate	1.28	289.14	*
473 	ethyl 4-({[(3-methylphenyl)amino]carbonyl} amino)benzoate	1.33	299.16	*
474 	ethyl 4-({[(4-methylphenyl)amino]carbonyl} amino)benzoate	1.33	299.16	*

Table 3

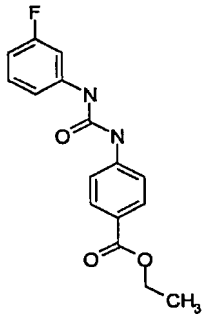
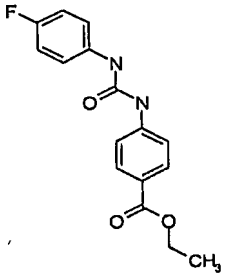
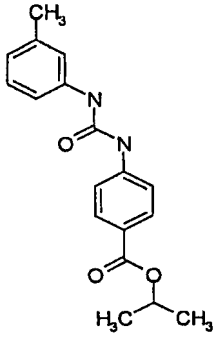
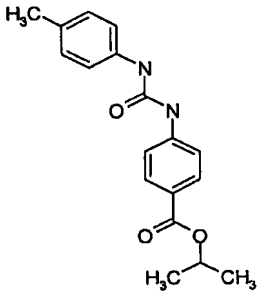
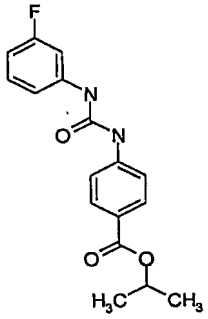
Compound	Name	R.T.	MS	IC50
475 	ethyl 4-({[(3-fluorophenyl)amino]carbonyl} amino)benzoate	1.33	303.14	*
476 	ethyl 4-({[(4-fluorophenyl)amino]carbonyl} amino)benzoate	1.31	303.14	*
477 	isopropyl 4-({[(3-methylphenyl)amino]carbonyl} amino)benzoate	1.36	313.18	*
478 	isopropyl 4-({[(4-methylphenyl)amino]carbonyl} amino)benzoate	1.35	313.18	*
479 	isopropyl 4-({[(3-fluorophenyl)amino]carbonyl} amino)benzoate	1.35	317.16	*

Table 3

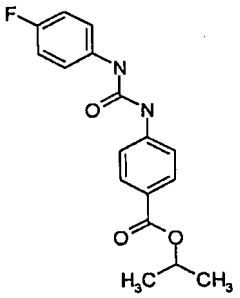
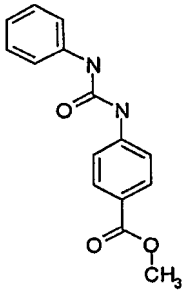
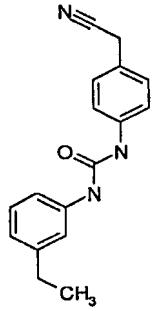
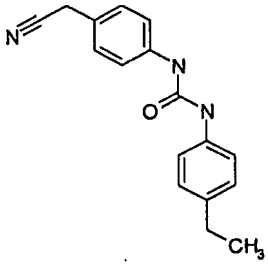
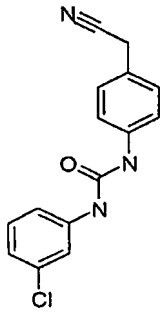
Compound	Name	R.T.	MS	IC50
480 	isopropyl 4-({[(4-fluorophenyl)amino]carbonyl} amino)benzoate	1.33	317.16	*
481 	methyl 4-[(anilinocarbonyl)amino]benzoate	1.27	271.14	*
482 	1-[4-(cyanomethyl)phenyl]-3-(3-ethylphenyl)urea	1.28	280.17	*
483 	1-[4-(cyanomethyl)phenyl]-3-(4-ethylphenyl)urea	1.27	280.18	*
484 	1-(3-chlorophenyl)-3-[4-(cyanomethyl)phenyl]urea	1.27	286.12	*

Table 3

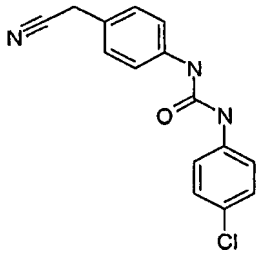
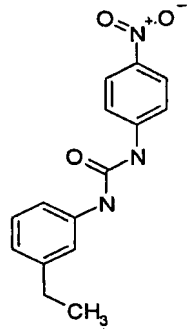
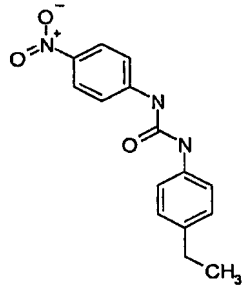
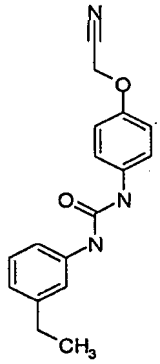
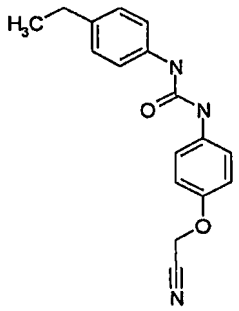
Compound	Name	R.T.	MS	IC50
485 	1-(4-chlorophenyl)-3-[4-(cyanomethyl)phenyl]urea	1.27	286.13	*
486 	1-(3-ethylphenyl)-3-(4-nitrophenyl)urea	1.36	286.17	
487 	1-(4-ethylphenyl)-3-(4-nitrophenyl)urea	1.36	286.17	*
488 	1-[4-(cyanomethoxy)phenyl]-3-(3-ethylphenyl)urea	1.28	296.17	*
489 	N-[4-(cyanomethoxy)phenyl]-N'-(4-ethylphenyl)urea	1.27	296.17	*

Table 3

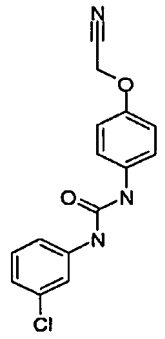
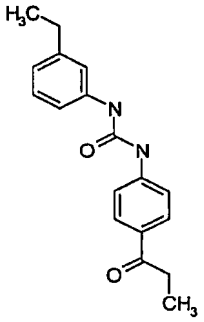
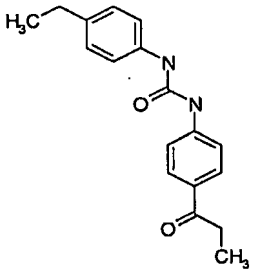
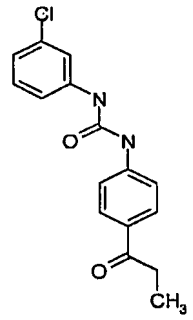
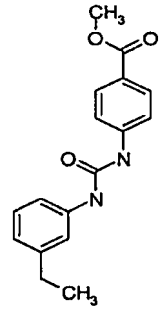
Compound	Name	R.T.	MS	IC50
490 	1-(3-chlorophenyl)-3-[4-(cyanomethoxy)phenyl]urea	1.28	302.12	*
491 	1-(3-ethylphenyl)-3-(4-propionylphenyl)urea	1.34	297.18	*
492 	1-(4-ethylphenyl)-3-(4-propionylphenyl)urea	1.34	297.18	*
493 	1-(3-chlorophenyl)-3-(4-propionylphenyl)urea	1.34	303.14	*
494 	methyl 4-({[(3-ethylphenyl)amino]carbonyl}amino)benzoate	1.34	299.17	*

Table 3

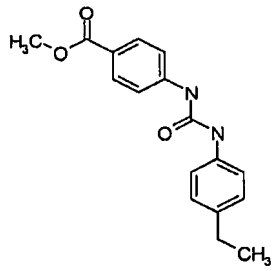
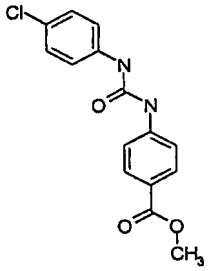
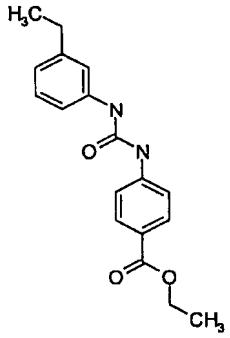
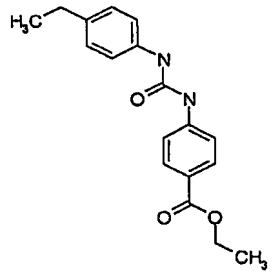
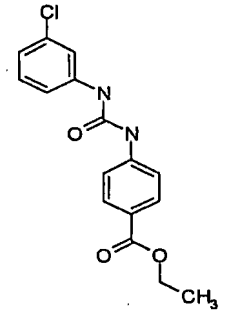
Compound	Name	R.T.	MS	IC50
495 	methyl 4-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate	1.34	299.17	*
496 	methyl 4-({[(4-chlorophenyl)amino]carbonyl}amino)benzoate	1.34	305.14	*
497 	ethyl 4-({[(3-ethylphenyl)amino]carbonyl}amino)benzoate	1.36	313.18	*
498 	ethyl 4-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate	1.37	313.19	*
499 	ethyl 4-({[(3-chlorophenyl)amino]carbonyl}amino)benzoate	1.37	319.14	*

Table 3

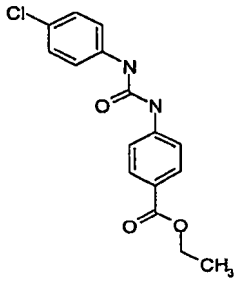
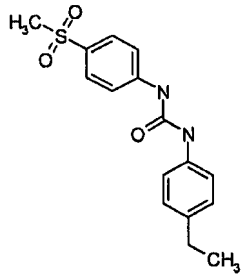
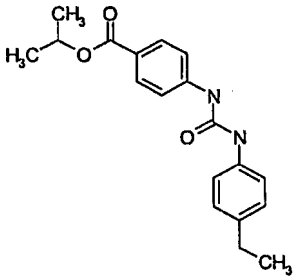
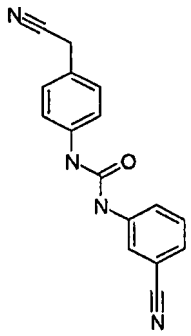
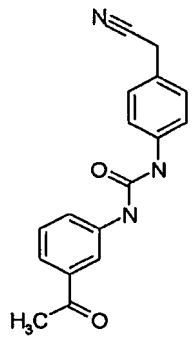
Compound	Name	R.T.	MS	IC50
500 	ethyl 4-({[(4-chlorophenyl)amino]carbonyl} amino)benzoate	1.36	319.15	*
501 	1-(4-ethylphenyl)-3-[4-(methylsulfonyl)phenyl]urea	1.26	319.16	*
502 	isopropyl 4-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate	1.38	327.21	*
503 	1-[4-(cyanomethyl)phenyl]-3-(3-cyanophenyl)urea	1.2	277.18	*
504 	1-(3-acetylphenyl)-3-[4-(cyanomethyl)phenyl]urea	1.19	294.18	*

Table 3

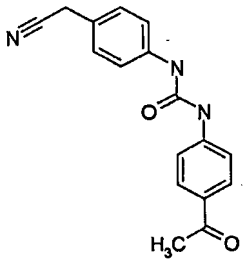
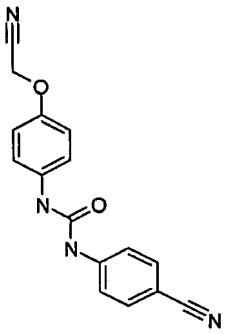
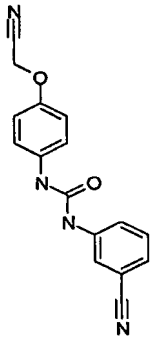
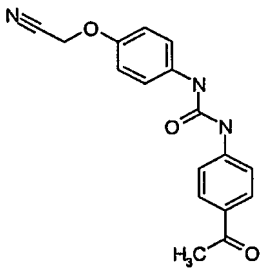
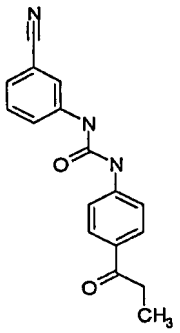
Compound	Name	R.T.	MS	IC50
505 	1-(4-acetylphenyl)-3-[4-(cyanomethyl)phenyl]urea	1.19	294.19	*
506 	1-[4-(cyanomethoxy)phenyl]-3-(4-cyanophenyl)urea	1.21	293.18	*
507 	1-[4-(cyanomethoxy)phenyl]-3-(3-cyanophenyl)urea	1.2	293.17	*
508 	1-(4-acetylphenyl)-3-[4-(cyanomethoxy)phenyl]urea	1.19	310.18	*
509 	1-(3-cyanophenyl)-3-(4-propionylphenyl)urea	1.27	294.2	*

Table 3

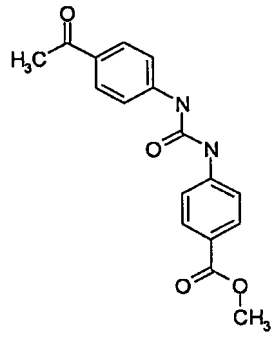
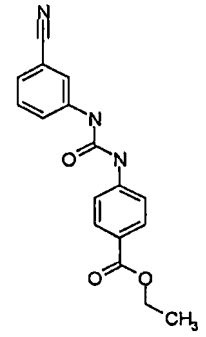
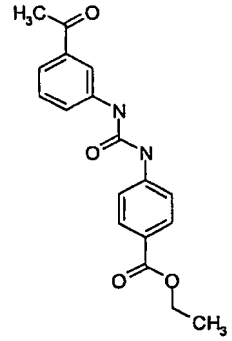
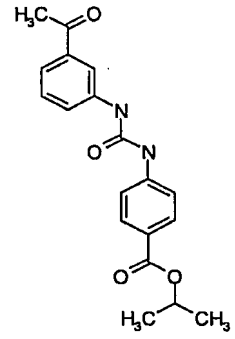
Compound	Name	R.T.	MS	IC50
510 	methyl 4-({[(4-acetylphenyl)amino]carbonyl}amino)benzoate	1.27	313.19	*
511 	ethyl 4-({[(3-cyanophenyl)amino]carbonyl}amino)benzoate	1.3	310.18	*
512 	ethyl 4-({[(3-acetylphenyl)amino]carbonyl}amino)benzoate			*
513 	isopropyl 4-({[(3-acetylphenyl)amino]carbonyl}amino)benzoate	1.32	341.21	*

Table 3

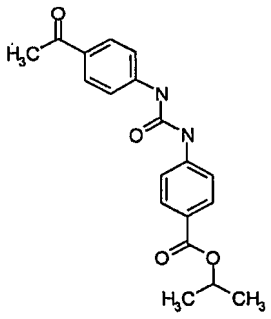
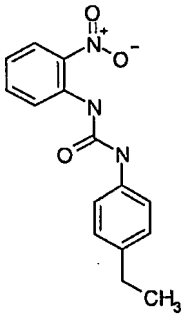
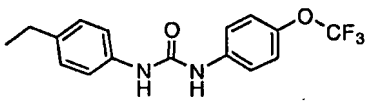
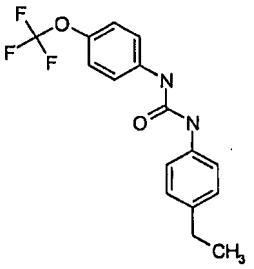
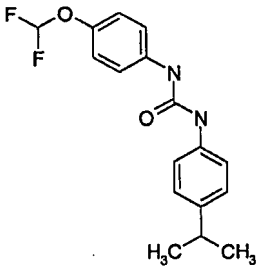
	Compound	Name	R.T.	MS	IC50
514		isopropyl 4-({[(4-acetylphenyl)amino]carbonyl}amino)benzoate	1.32	341.2	*
515		1-(4-ethylphenyl)-3-(2-nitrophenyl)urea			*
516		N-(3-ethylphenyl)-N'-[4-(trifluoromethoxy)phenyl]urea	1.37	325.12	
517		1-(4-ethylphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.38	325.13	*
518		1-[4-(difluoromethoxy)phenyl]-3-(4-isopropylphenyl)urea	1.35	321.14	*

Table 3

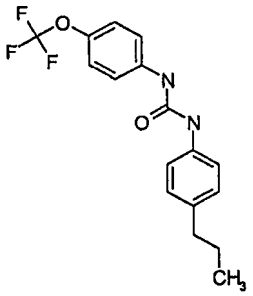
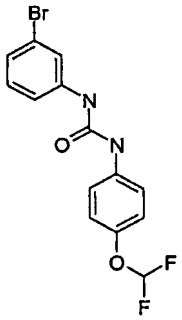
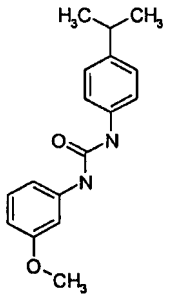
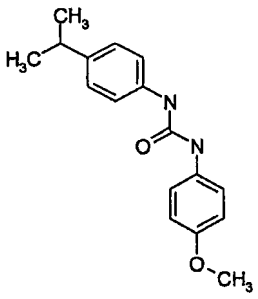
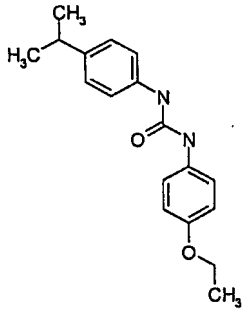
Compound	Name	R.T.	MS	IC50
519		1-(4-propylphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.4	339.14	*
520		1-(3-bromophenyl)-3-[4-(difluoromethoxy)phenyl]urea	1.32	357.03	*
521		1-(4-isopropylphenyl)-3-(3-methoxyphenyl)urea	1.33	285.15	*
522		1-(4-isopropylphenyl)-3-(4-methoxyphenyl)urea	1.32	285.15	*
523		1-(4-ethoxyphenyl)-3-(4-isopropylphenyl)urea	1.35	299.17	

Table 3

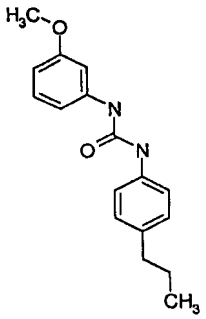
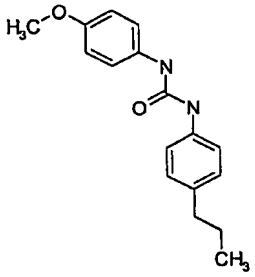
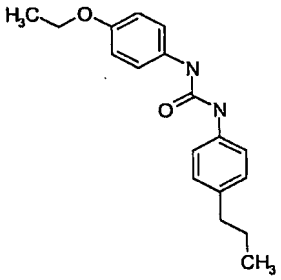
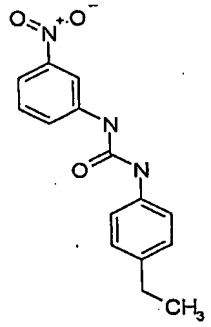
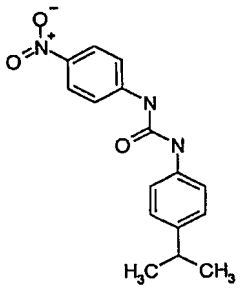
Compound	Name	R.T.	MS	IC50
524 	1-(3-methoxyphenyl)-3-(4-propylphenyl)urea	1.35	285.15	*
525 	1-(4-methoxyphenyl)-3-(4-propylphenyl)urea	1.33	285.15	*
526 	1-(4-ethoxyphenyl)-3-(4-propylphenyl)urea	1.36	299.17	*
527 	1-(4-ethylphenyl)-3-(3-nitrophenyl)urea	1.34	286.12	*
528 	1-(4-isopropylphenyl)-3-(4-nitrophenyl)urea	1.37	300.15	*

Table 3

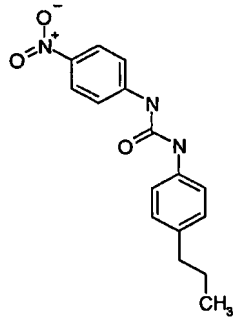
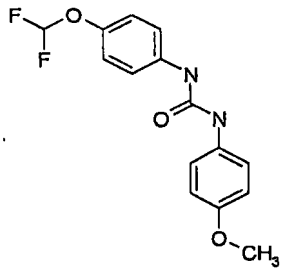
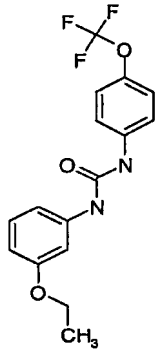
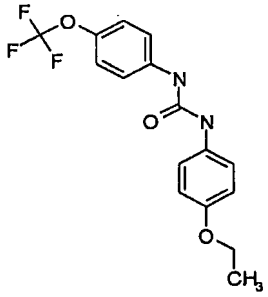
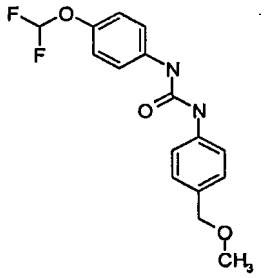
Compound	Name	R.T.	MS	IC50
529 	1-(4-nitrophenyl)-3-(4-propylphenyl)urea	1.39	300.15	*
530 	1-[4-(difluoromethoxy)phenyl]-3-(4-methoxyphenyl)urea	1.25	309.11	*
531 	1-(3-ethoxyphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.36	341.09	*
532 	1-(4-ethoxyphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.34	341.1	*
533 	1-[4-(difluoromethoxy)phenyl]-3-[4-(methoxymethyl)phenyl]urea	1.26	323.11	*

Table 3

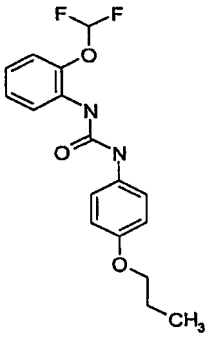
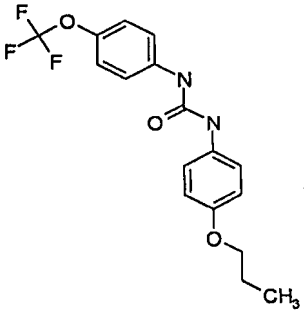
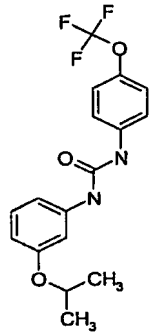
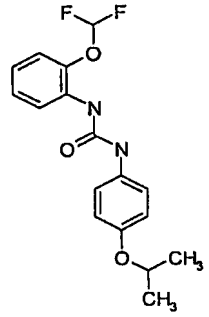
Compound	Name	R.T.	MS	IC50
534 	1-[2-(difluoromethoxy)phenyl]-3-(4-propoxyphenyl)urea	1.34	337.12	*
535 	1-(4-propoxyphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.38	355.13	*
536 	1-(3-isopropoxyphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.37	355.11	*
537 	1-[2-(difluoromethoxy)phenyl]-3-(4-isopropoxyphenyl)urea	1.32	337.12	*

Table 3

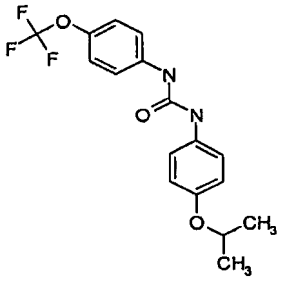
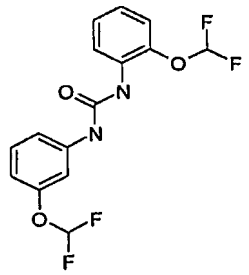
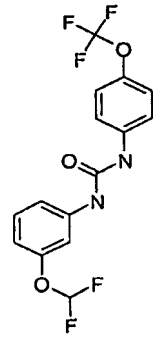
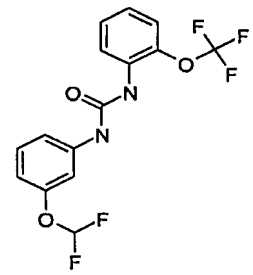
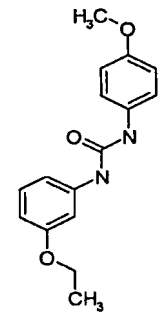
Compound	Name	R.T.	MS	IC50
538 	1-(4-isopropoxyphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.37	355.12	*
539 	1-[2-(difluoromethoxy)phenyl]-3-[3-(difluoromethoxy)phenyl]urea	1.31	345.07	*
540 	1-[3-(difluoromethoxy)phenyl]-3-[4-(trifluoromethoxy)phenyl]urea	1.35	363.07	*
541 	1-[3-(difluoromethoxy)phenyl]-3-[2-(trifluoromethoxy)phenyl]urea	1.35	363.06	*
542 	1-(3-ethoxyphenyl)-3-(4-methoxyphenyl)urea	1.26	287.13	*

Table 3

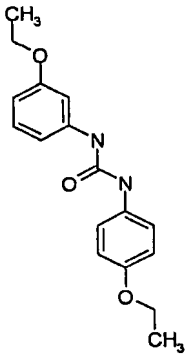
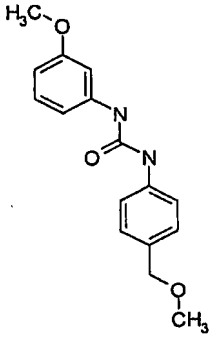
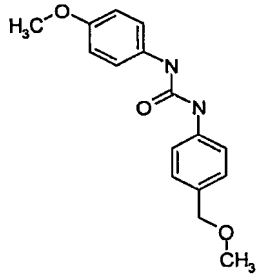
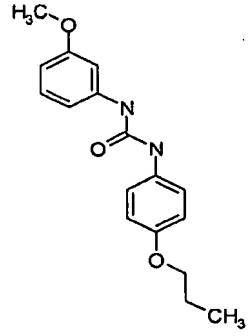
Compound	Name	R.T.	MS	IC50
543 	1-(3-ethoxyphenyl)-3-(4-ethoxyphenyl)urea	1.29	301.14	*
544 	1-[4-(methoxymethyl)phenyl]-3-(3-methoxyphenyl)urea	1.24	287.13	*
545 	1-[4-(methoxymethyl)phenyl]-3-(4-methoxyphenyl)urea	1.22	287.13	*
546 	1-(3-methoxyphenyl)-3-(4-propoxyphenyl)urea	1.31	301.14	*

Table 3

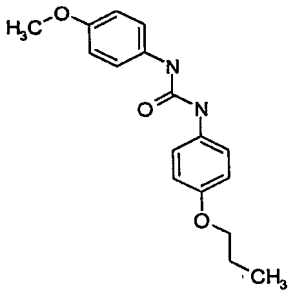
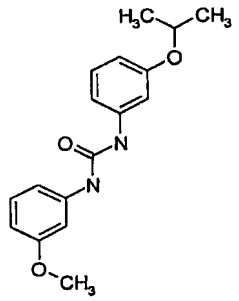
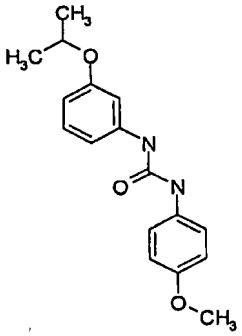
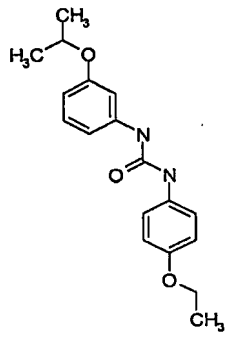
Compound	Name	R.T.	MS	IC50
547 	1-(4-methoxyphenyl)-3-(4-propoxyphenyl)urea	1.29	301.14	*
548 	1-(3-isopropoxyphenyl)-3-(3-methoxyphenyl)urea	1.3	301.14	*
549 	1-(3-isopropoxyphenyl)-3-(4-methoxyphenyl)urea	1.28	301.14	*
550 	1-(4-ethoxyphenyl)-3-(3-isopropoxyphenyl)urea	1.32	315.15	*

Table 3

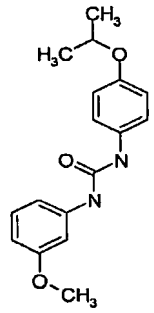
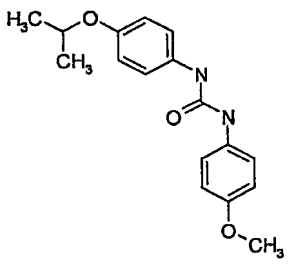
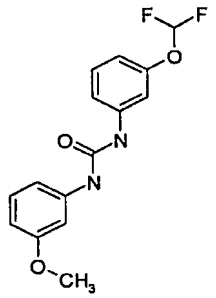
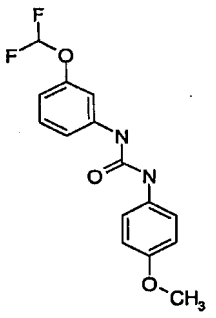
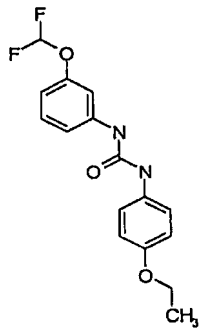
Compound	Name	R.T.	MS	IC50
551 	1-(4-isopropoxyphenyl)-3-(3-methoxyphenyl)urea	1.29	301.14	*
552 	1-(4-isopropoxyphenyl)-3-(4-methoxyphenyl)urea	1.27	301.14	*
553 	1-[3-(difluoromethoxy)phenyl]-3-(3-methoxyphenyl)urea	1.28	309.09	*
554 	1-[3-(difluoromethoxy)phenyl]-3-(4-methoxyphenyl)urea	1.26	309.1	*
555 	1-[3-(difluoromethoxy)phenyl]-3-(4-ethoxyphenyl)urea	1.29	323.11	*

Table 3

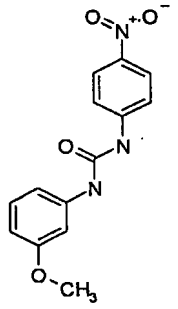
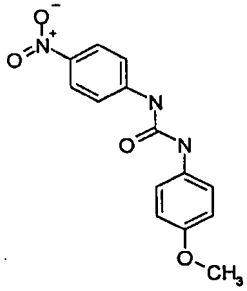
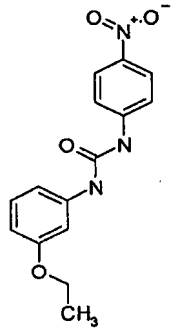
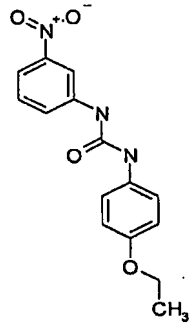
Compound	Name	R.T.	MS	IC50
556 	1-(3-methoxyphenyl)-3-(4-nitrophenyl)urea	1.28	288.11	*
557 	1-(4-methoxyphenyl)-3-(4-nitrophenyl)urea	1.26	288.1	*
558 	1-(3-ethoxyphenyl)-3-(4-nitrophenyl)urea	1.32	302.12	*
559 	1-(4-ethoxyphenyl)-3-(3-nitrophenyl)urea	1.29	302.12	*

Table 3

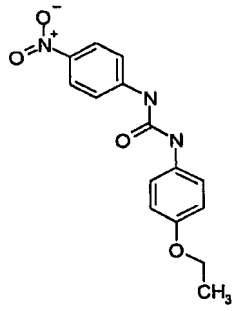
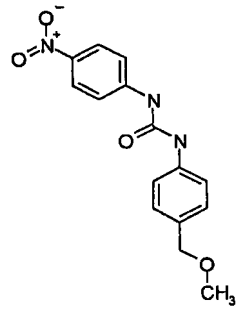
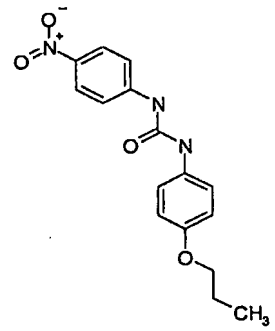
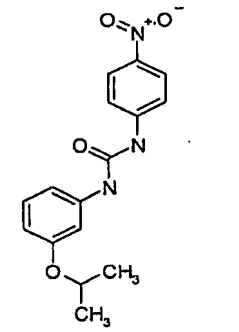
Compound	Name	R.T.	MS	IC50
560 	1-(4-ethoxyphenyl)-3-(4-nitrophenyl)urea	1.3	302.12	*
561 	1-[4-(methoxymethyl)phenyl]-3-(4-nitrophenyl)urea	1.28	302.11	*
562 	1-(4-nitrophenyl)-3-(4-propoxyphenyl)urea	1.34	316.14	*
563 	1-(3-isopropoxyphenyl)-3-(4-nitrophenyl)urea	1.34	316.13	*

Table 3

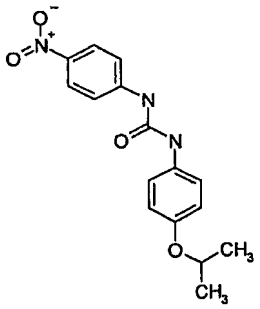
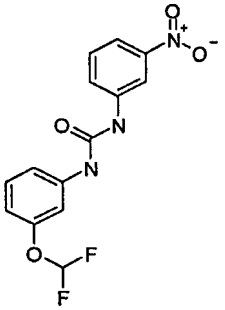
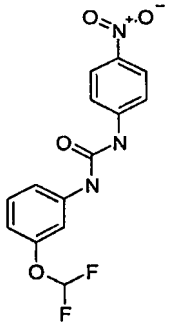
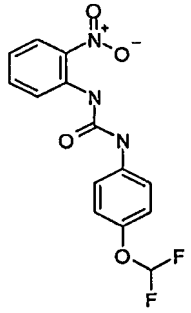
Compound	Name	R.T.	MS	IC50
564 	1-(4-isopropoxyphenyl)-3-(4-nitrophenyl)urea	1.32	316.13	*
565 	1-[3-(difluoromethoxy)phenyl]-3-(3-nitrophenyl)urea	1.29	324.12	*
566 	1-[3-(difluoromethoxy)phenyl]-3-(4-nitrophenyl)urea	1.31	324.1	*
567 	1-[4-(difluoromethoxy)phenyl]-3-(2-nitrophenyl)urea	1.32	324.09	

Table 3

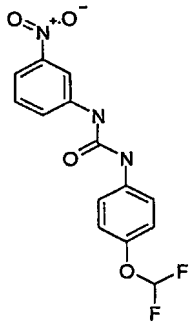
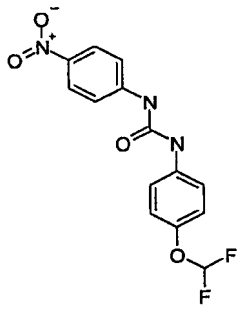
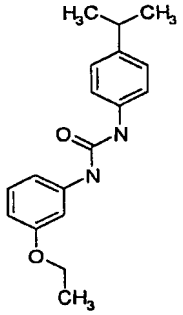
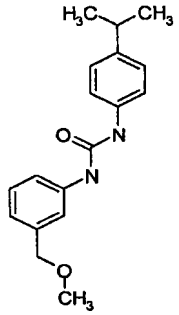
Compound	Name	R.T.	MS	IC50
568 	1-[4-(difluoromethoxy)phenyl]-3-(3-nitrophenyl)urea	1.29	324.09	*
569 	1-[4-(difluoromethoxy)phenyl]-3-(4-nitrophenyl)urea	1.3	324.12	*
570 	1-(3-ethoxyphenyl)-3-(4-isopropylphenyl)urea	1.36	299.15	*
571 	1-(4-isopropylphenyl)-3-[3-(methoxymethyl)phenyl]urea	1.33	299.16	*

Table 3

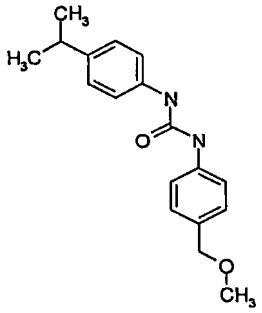
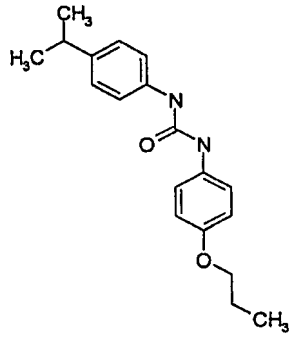
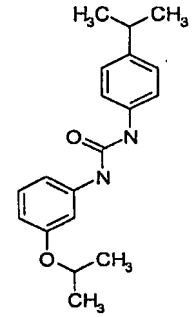
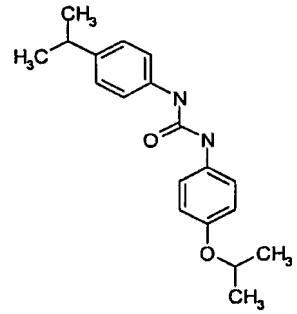
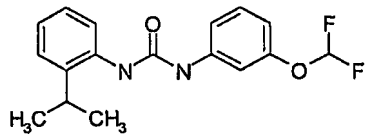
Compound	Name	R.T.	MS	IC50
572 	1-(4-isopropylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.33	299.15	*
573 	1-(4-isopropylphenyl)-3-(4-propoxyphenyl)urea	1.39	313.17	*
574 	1-(3-isopropoxyphenyl)-3-(4-isopropylphenyl)urea	1.38	313.17	*
575 	1-(4-isopropoxyphenyl)-3-(4-isopropylphenyl)urea	1.37	313.17	*
576 	1-[3-(difluoromethoxy)phenyl]-3-(2-isopropylphenyl)urea	1.33	321.12	*

Table 3

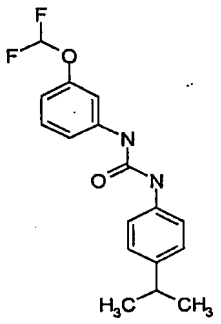
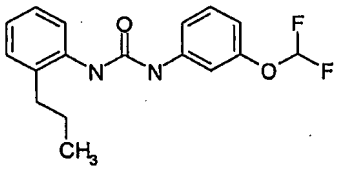
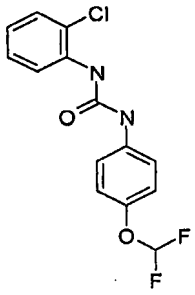
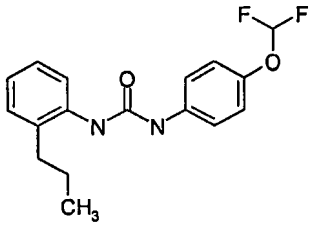
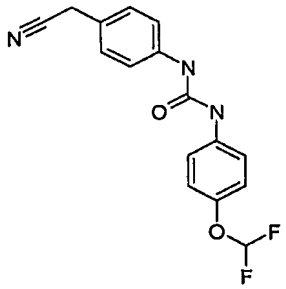
Compound	Name	R.T.	MS	IC50
577 	1-[3-(difluoromethoxy)phenyl]-3-(4-isopropylphenyl)urea	1.36	321.13	*
578 	1-[3-(difluoromethoxy)phenyl]-3-(2-propylphenyl)urea	1.33	321.12	*
579 	1-(2-chlorophenyl)-3-[4-(difluoromethoxy)phenyl]urea	1.31	313.05	
580 	1-[4-(difluoromethoxy)phenyl]-3-(2-propylphenyl)urea	1.33	321.13	
581 	1-[4-(cyanomethyl)phenyl]-3-[4-(difluoromethoxy)phenyl]urea	1.14	318.18	*

Table 3

Compound	Name	R.T.	MS	IC50
582	1-[4-(cyanomethoxy)phenyl]-3-[4-(difluoromethoxy)phenyl]urea	1.14	334.2	*
583	ethyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.23	351.22	*
584	isopropyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.25	365.24	*
585	1-[4-(cyanomethyl)phenyl]-3-(3-methoxyphenyl)urea	1.12	282.2	*
586	1-[4-(cyanomethyl)phenyl]-3-(4-methoxyphenyl)urea	1.1	282.2	*

Table 3

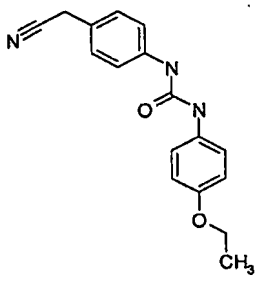
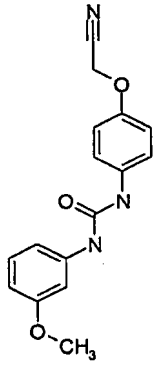
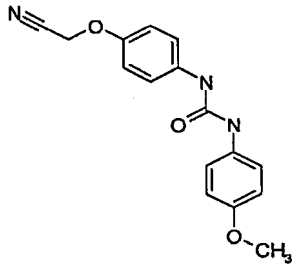
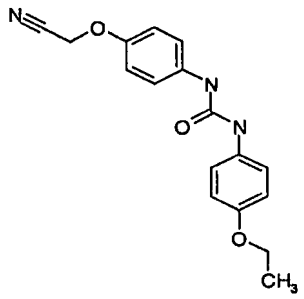
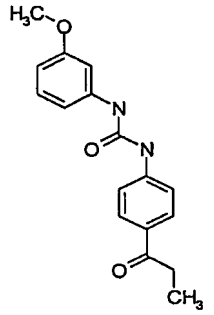
Compound	Name	R.T.	MS	IC50
587 	1-[4-(cyanomethyl)phenyl]-3-(4-ethoxyphenyl)urea	1.15	296.22	*
588 	1-[4-(cyanomethoxy)phenyl]-3-(3-methoxyphenyl)urea	1.13	298.2	*
589 	1-[4-(cyanomethoxy)phenyl]-3-(4-methoxyphenyl)urea	1.11	298.19	*
590 	1-[4-(cyanomethoxy)phenyl]-3-(4-ethoxyphenyl)urea	1.15	312.22	*
591 	1-(3-methoxyphenyl)-3-(4-propionylphenyl)urea	1.19	299.21	*

Table 3

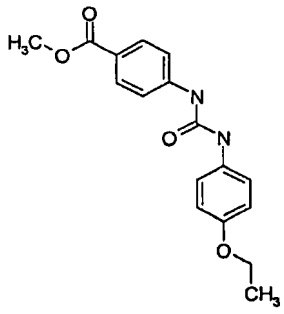
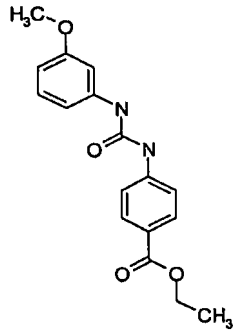
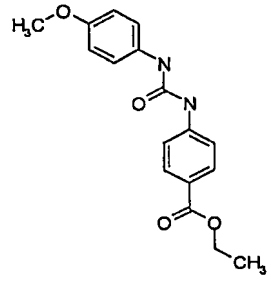
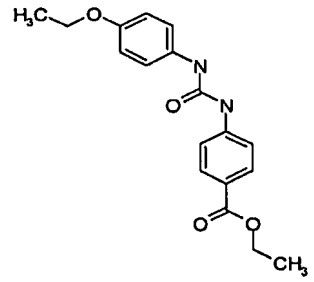
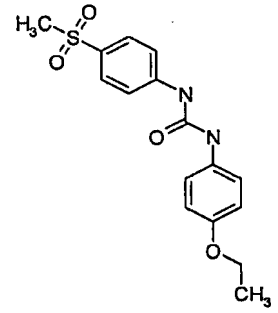
Compound	Name	R.T.	MS	IC50
592 	methyl 4-({[(4-ethoxyphenyl)amino]carbonyl}amino)benzoate	1.21	315.21	
593 	ethyl 4-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate	1.22	315.21	*
594 	ethyl 4-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate			*
595 	ethyl 4-({[(4-ethoxyphenyl)amino]carbonyl}amino)benzoate	1.24	329.23	*
596 	1-(4-ethoxyphenyl)-3-[4-(methylsulfonyl)phenyl]urea	1.13	335.19	*

Table 3

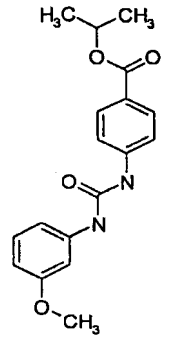
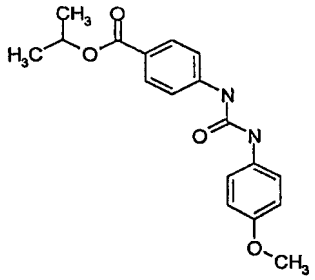
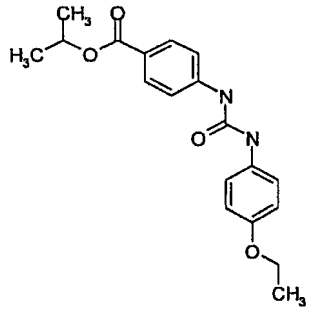
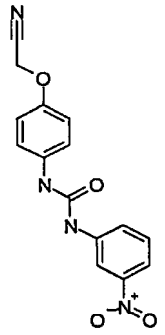
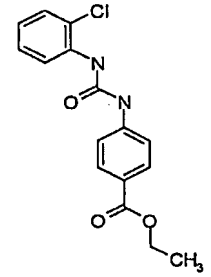
Compound		Name	R.T.	MS	IC50
597		isopropyl 4-({[(3-methoxyphenyl)amino]carbonyl}amino)benzoate	1.25	329.23	*
598		isopropyl 4-({[(4-methoxyphenyl)amino]carbonyl}amino)benzoate	1.23	329.23	*
599		isopropyl 4-({[(4-ethoxyphenyl)amino]carbonyl}amino)benzoate	1.26	343.25	*
600		1-[4-(cyanomethoxy)phenyl]-3-(3-nitrophenyl)urea			*
601		ethyl 4-({[(2-chlorophenyl)amino]carbonyl}amino)benzoate	1.27	319.18	

Table 3

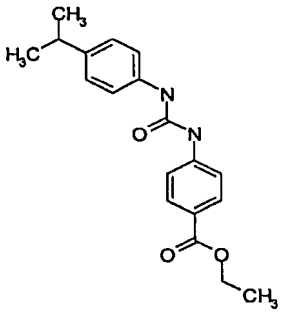
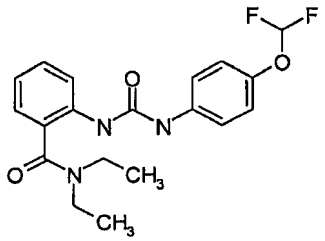
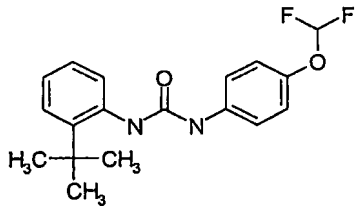
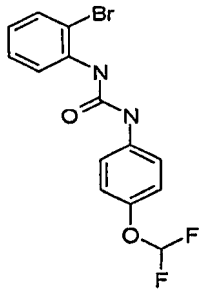
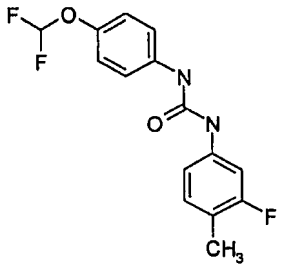
Compound	Name	R.T.	MS	IC50
602 	ethyl 4-({[(4-isopropylphenyl)amino]carbonyl}amino)benzoate			*
603 	2-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]-N,N-diethylbenzamide	1.19	378.26	*
604 	1-(2-tert-butylphenyl)-3-[4-(difluoromethoxy)phenyl]urea	1.23	335.24	*
605 	1-(2-bromophenyl)-3-[4-(difluoromethoxy)phenyl]urea			*
606 	1-[4-(difluoromethoxy)phenyl]-3-(3-fluoro-4-methylphenyl)urea	1.24	311.17	*

Table 3

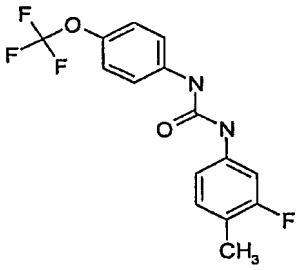
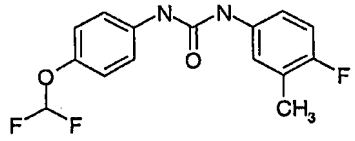
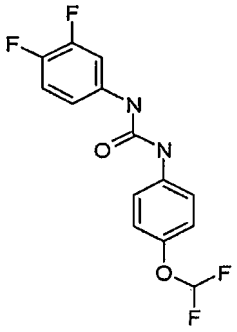
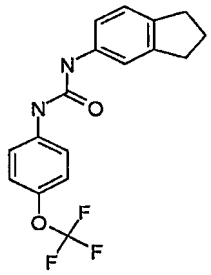
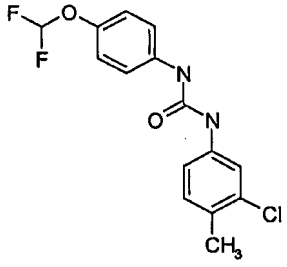
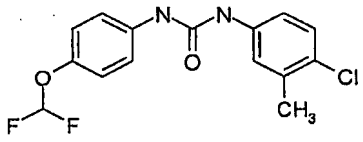
Compound	Name	R.T.	MS	IC50
607		1-(3-fluoro-4-methylphenyl)-3-[4-(trifluoromethoxy)phenyl]urea	1.29	329.17	*
608		1-[4-(difluoromethoxy)phenyl]-3-(4-fluoro-3-methylphenyl)urea	1.22	311.18	*
609		1-[4-(difluoromethoxy)phenyl]-3-(3,4-difluorophenyl)urea	1.29	315.14	*
610		1-(2,3-dihydro-1H-inden-5-yl)-3-[4-(trifluoromethoxy)phenyl]urea	1.31	337.21	*
611		1-(3-chloro-4-methylphenyl)-3-[4-(difluoromethoxy)phenyl]urea	1.26	327.17	*
612		1-(4-chloro-3-methylphenyl)-3-[4-(difluoromethoxy)phenyl]urea	1.26	327.16	*

Table 3

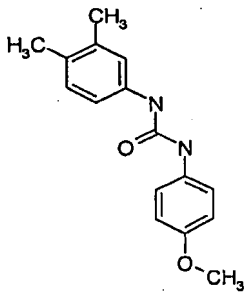
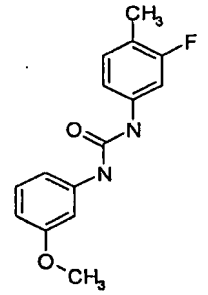
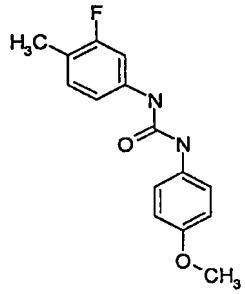
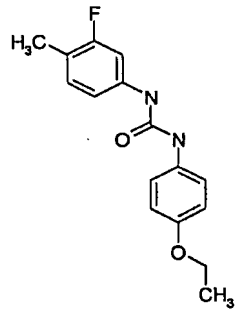
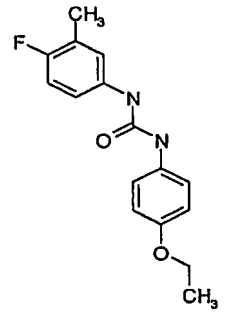
Compound	Name	R.T.	MS	IC50
613 	1-(3,4-dimethylphenyl)-3-(4-methoxyphenyl)urea	1.21	271.22	
614 	1-(3-fluoro-4-methylphenyl)-3-(3-methoxyphenyl)urea	1.22	275.2	*
615 	1-(3-fluoro-4-methylphenyl)-3-(4-methoxyphenyl)urea	1.2	275.2	*
616 	1-(4-ethoxyphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.23	289.22	*
617 	1-(4-ethoxyphenyl)-3-(4-fluoro-3-methylphenyl)urea	1.22	289.22	*

Table 3

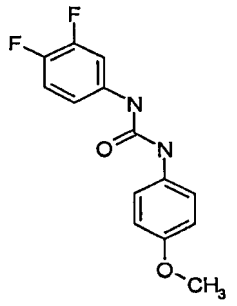
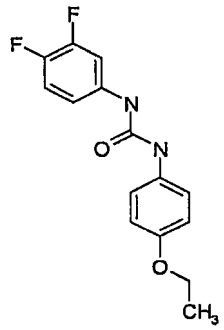
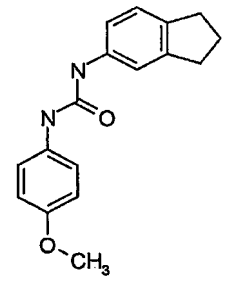
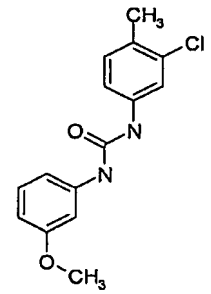
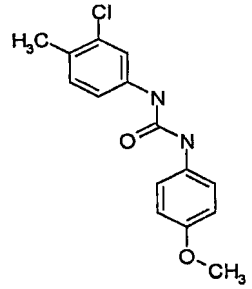
Compound	Name	R.T.	MS	IC50
618 	1-(3,4-difluorophenyl)-3-(4-methoxyphenyl)urea	1.19	279.18	
619 	1-(3,4-difluorophenyl)-3-(4-ethoxyphenyl)urea	1.21	293.2	*
620 	1-(2,3-dihydro-1H-inden-5-yl)-3-(4-methoxyphenyl)urea	1.22	283.22	*
621 	1-(3-chloro-4-methylphenyl)-3-(3-methoxyphenyl)urea	1.25	291.17	*
622 	1-(3-chloro-4-methylphenyl)-3-(4-methoxyphenyl)urea	1.24	291.18	*

Table 3

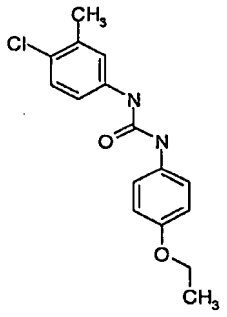
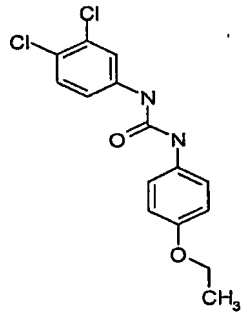
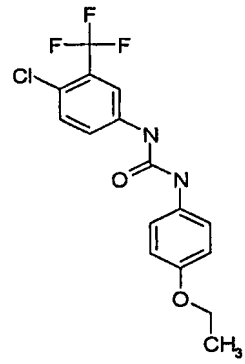
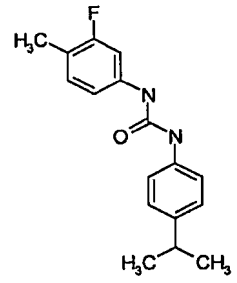
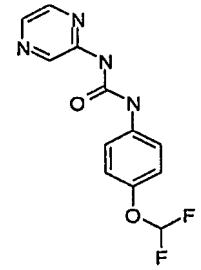
Compound	Name	R.T.	MS	IC50
623 	1-(4-chloro-3-methylphenyl)-3-(4-ethoxyphenyl)urea	1.26	305.2	*
624 	1-(3,4-dichlorophenyl)-3-(4-ethoxyphenyl)urea	1.28	325.14	*
625 	1-[4-chloro-3-(trifluoromethyl)phenyl]-3-(4-ethoxyphenyl)urea	1.28	359.19	*
626 	1-(3-fluoro-4-methylphenyl)-3-(4-isopropylphenyl)urea	1.29	287.23	*
627 	1-[4-(difluoromethoxy)phenyl]-3-pyrazin-2-ylurea	1.22	281.14	*

Table 3

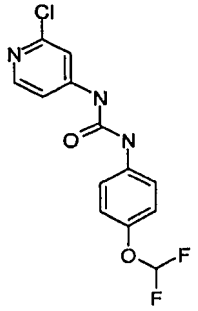
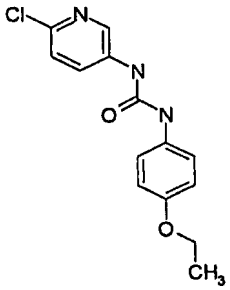
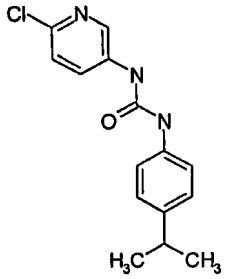
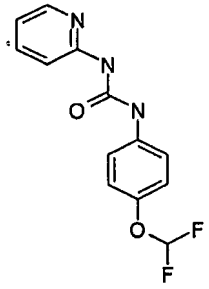
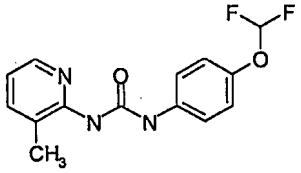
Compound	Name	R.T.	MS	IC50
628 	1-(2-chloropyridin-4-yl)-3-[4-(difluoromethoxy)phenyl]urea	1.27	314.11	*
629 	1-(6-chloropyridin-3-yl)-3-(4-ethoxyphenyl)urea	1.26	292.11	*
630 	1-(6-chloropyridin-3-yl)-3-(4-isopropylphenyl)urea	1.34	290.13	*
631 	1-[4-(difluoromethoxy)phenyl]-3-pyridin-2-ylurea	1.18	280.12	*
632 	1-[4-(difluoromethoxy)phenyl]-3-(3-methylpyridin-2-yl)urea	1.14	294.13	*

Table 3

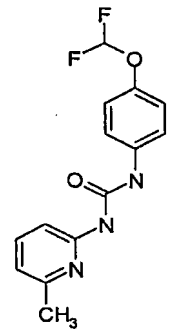
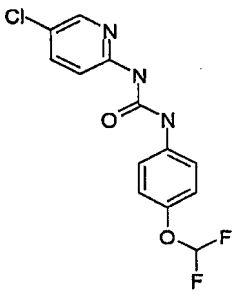
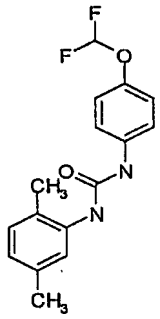
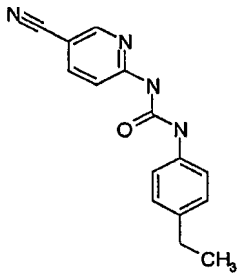
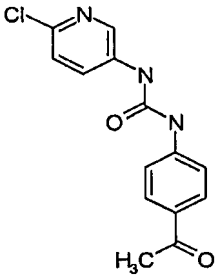
Compound	Name	R.T.	MS	IC50
633 	1-[4-(difluoromethoxy)phenyl]-3-(6-methylpyridin-2-yl)urea	1.23	294.13	*
634 	1-(5-chloropyridin-2-yl)-3-[4-(difluoromethoxy)phenyl]urea	1.34	314.09	*
635 	1-[4-(difluoromethoxy)phenyl]-3-(2,5-dimethylphenyl)urea	1.22	307.15	
636 	1-(5-cyanopyridin-2-yl)-3-(4-ethylphenyl)urea	1.24	267.15	*
637 	1-(4-acetylphenyl)-3-(6-chloropyridin-3-yl)urea	1.15	290.09	*

Table 3

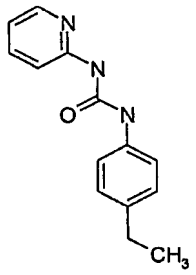
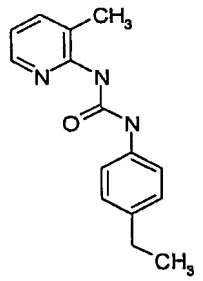
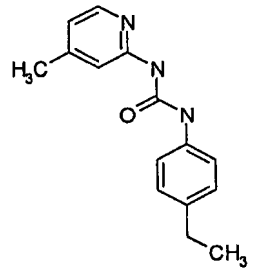
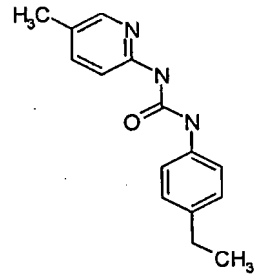
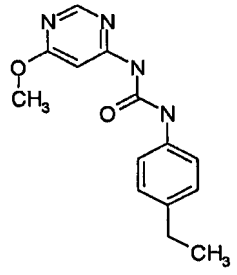
Compound	Name	R.T.	MS	IC50
638 	1-(4-ethylphenyl)-3-pyridin-2-ylurea	1.17	242.12	*
639 	1-(4-ethylphenyl)-3-(3-methylpyridin-2-yl)urea	1.12	256.14	*
640 	1-(4-ethylphenyl)-3-(4-methylpyridin-2-yl)urea	1.14	256.14	*
641 	1-(4-ethylphenyl)-3-(5-methylpyridin-2-yl)urea	1.18	256.14	*
642 	1-(4-ethylphenyl)-3-(6-methoxypyrimidin-4-yl)urea	1.27	273.13	*

Table 3

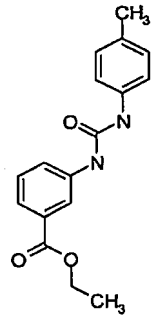
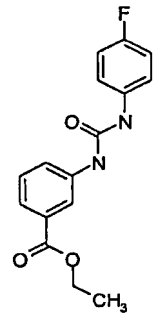
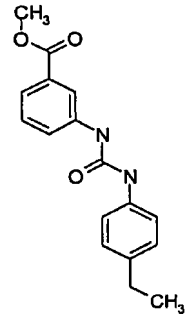
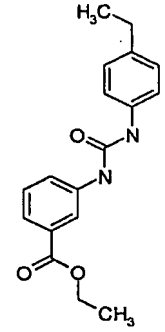
Compound	Name	R.T.	MS	IC50
643 	ethyl 3-({[(4-methylphenyl)amino]carbonyl}amino)benzoate			*
644 	ethyl 3-({[(4-fluorophenyl)amino]carbonyl}amino)benzoate	1.22	303.15	*
645 	methyl 3-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate			*
646 	ethyl 3-({[(4-ethylphenyl)amino]carbonyl}amino)benzoate			*

Table 3

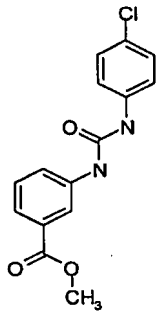
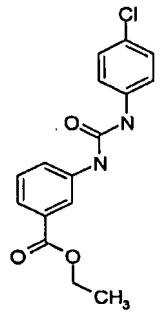
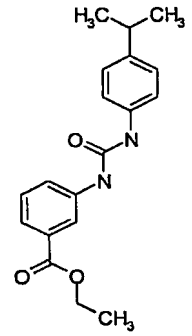
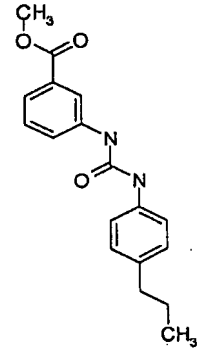
Compound	Name	R.T.	MS	IC50
647 	methyl 3-({[(4-chlorophenyl)amino]carbonyl} amino)benzoate	1.24	305.11	*
648 	ethyl 3-({[(4-chlorophenyl)amino]carbonyl} amino)benzoate	1.29	319.12	*
649 	ethyl 3-({[(4-isopropylphenyl)amino]carbonyl}amino)benzoate			*
650 	methyl 3-({[(4-propylphenyl)amino]carbonyl} amino)benzoate			*

Table 3

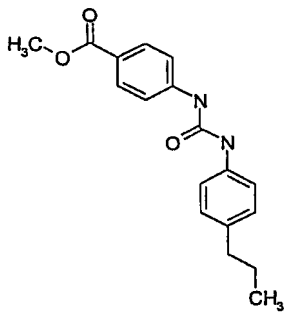
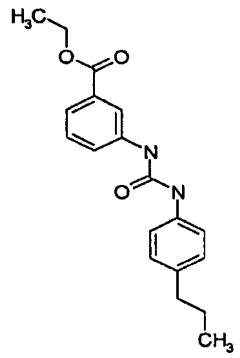
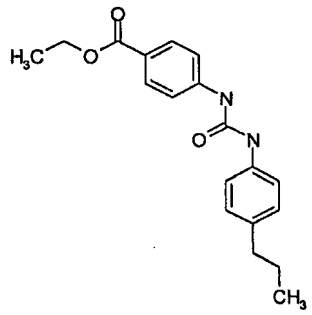
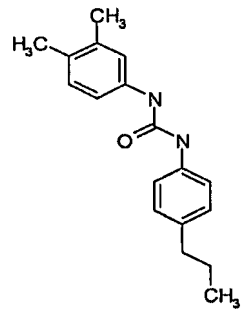
Compound	Name	R.T.	MS	IC50
651 	methyl 4-({[(4-propylphenyl)amino]carbonyl} amino)benzoate			*
652 	ethyl 3-({[(4-propylphenyl)amino]carbonyl} amino)benzoate			*
653 	ethyl 4-({[(4-propylphenyl)amino]carbonyl} amino)benzoate			*
654 	1-(3,4-dimethylphenyl)-3-(4-propylphenyl)urea	1.3	283.21	*

Table 3

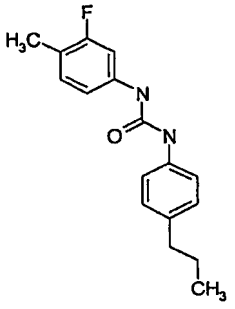
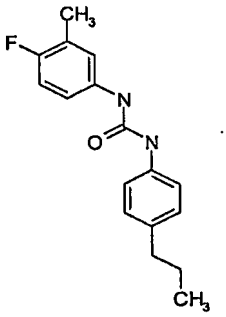
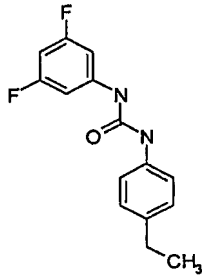
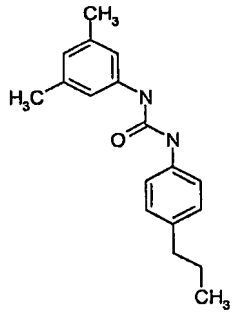
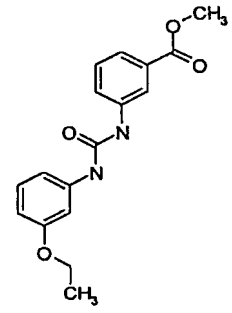
Compound	Name	R.T.	MS	IC50
655 	1-(3-fluoro-4-methylphenyl)-3-(4-propylphenyl)urea	1.3	287.19	*
656 	1-(4-fluoro-3-methylphenyl)-3-(4-propylphenyl)urea	1.29	287.19	*
657 	1-(3,5-difluorophenyl)-3-(4-ethylphenyl)urea	1.28	277.15	*
658 	1-(3,5-dimethylphenyl)-3-(4-propylphenyl)urea	1.32	283.22	*
659 	methyl 3-({[(3-ethoxyphenyl)amino]carbonyl}amino)benzoate	1.22	315.17	*

Table 3

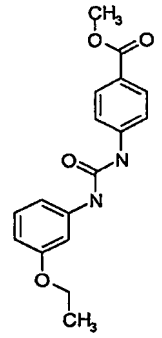
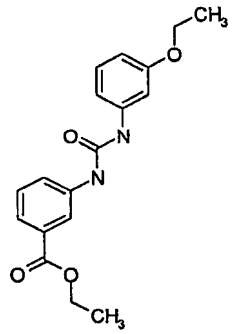
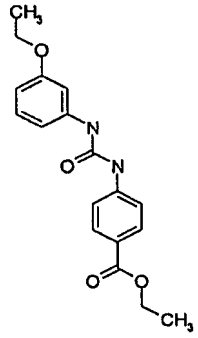
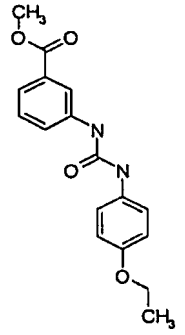
Compound	Name	R.T.	MS	IC50
660 	methyl 4-({[(3-ethoxyphenyl)amino]carbonyl} amino)benzoate	1.22	315.17	*
661 	ethyl 3-({[(3-ethoxyphenyl)amino]carbonyl} amino)benzoate	1.23	329.19	*
662 	ethyl 4-({[(3-ethoxyphenyl)amino]carbonyl} amino)benzoate	1.25	329.19	*
663 	methyl 3-({[(4-ethoxyphenyl)amino]carbonyl} amino)benzoate	1.2	315.18	*

Table 3

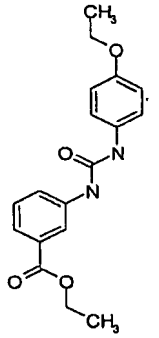
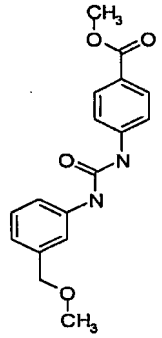
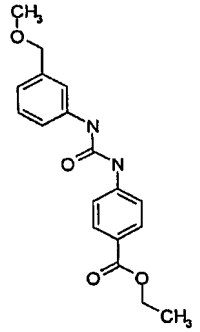
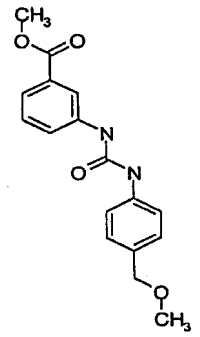
Compound	Name	R.T.	MS	IC50
664 	ethyl 3-({[(4-ethoxyphenyl)amino]carbonyl} amino)benzoate	1.23	329.19	*
665 	methyl 4-[({[3-(methoxymethyl)phenyl]amino }carbonyl)amino]benzoate	1.19	315.17	*
666 	ethyl 4-[({[3-(methoxymethyl)phenyl]amino }carbonyl)amino]benzoate	1.21	329.19	*
667 	methyl 3-[({[4-(methoxymethyl)phenyl]amino }carbonyl)amino]benzoate	1.18	315.17	*

Table 3

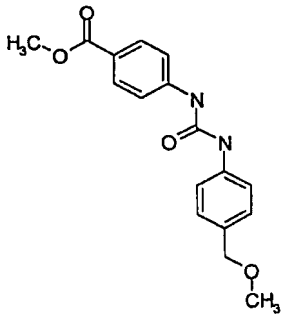
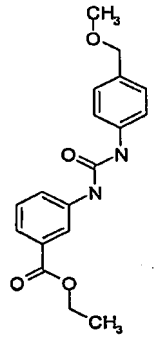
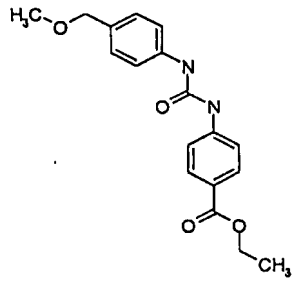
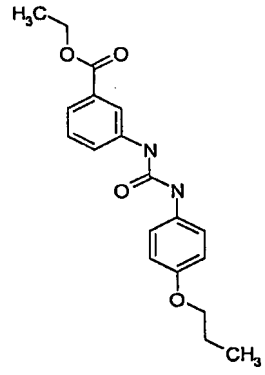
Compound	Name	R.T.	MS	IC50
668 	methyl 4-[({[4-(methoxymethyl)phenyl]amino}carbonyl)amino]benzoate	1.18	315.17	*
669 	ethyl 3-[({[4-(methoxymethyl)phenyl]amino}carbonyl)amino]benzoate	1.21	329.19	*
670 	ethyl 4-[({[4-(methoxymethyl)phenyl]amino}carbonyl)amino]benzoate	1.22	329.19	*
671 	ethyl 3-({[(4-propoxyphenyl)amino]carbonyl}amino)benzoate	1.26	343.2	*

Table 3

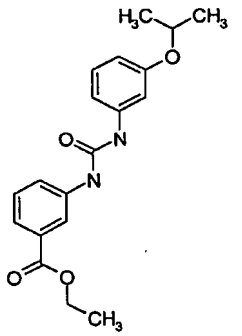
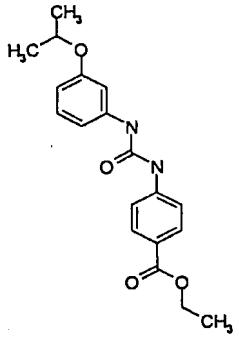
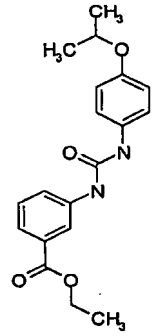
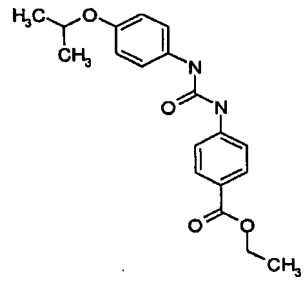
Compound	Name	R.T.	MS	IC50
672 	ethyl 3-({[(3-isopropoxyphenyl)amino]carbonyl}amino)benzoate	1.26	343.19	*
673 	ethyl 4-({[(3-isopropoxyphenyl)amino]carbonyl}amino)benzoate	1.27	343.19	*
674 	ethyl 3-({[(4-isopropoxyphenyl)amino]carbonyl}amino)benzoate	1.24	343.18	*
675 	ethyl 4-({[(4-isopropoxyphenyl)amino]carbonyl}amino)benzoate	1.26	343.19	*

Table 3

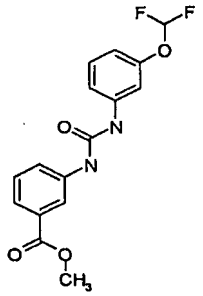
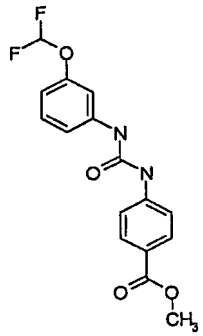
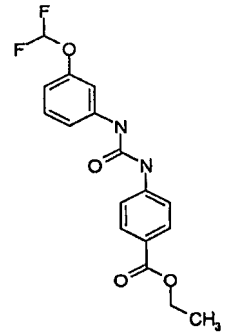
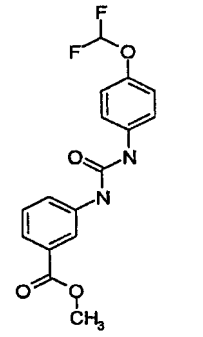
Compound	Name	R.T.	MS	IC50
676 	methyl 3-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.21	337.12	*
677 	methyl 4-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.21	337.13	*
678 	ethyl 4-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.24	351.14	*
679 	methyl 3-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.2	337.12	*

Table 3

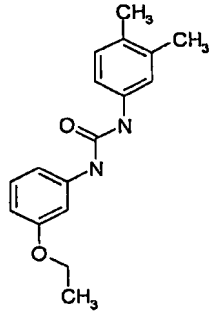
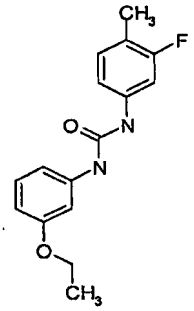
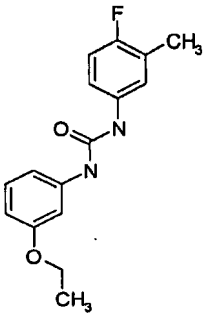
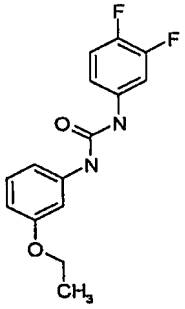
Compound	Name	R.T.	MS	IC50
680 	1-(3,4-dimethylphenyl)-3-(3-ethoxyphenyl)urea	1.25	285.18	*
681 	1-(3-ethoxyphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.25	289.16	*
682 	1-(3-ethoxyphenyl)-3-(4-fluoro-3-methylphenyl)urea	1.23	289.16	*
683 	1-(3,4-difluorophenyl)-3-(3-ethoxyphenyl)urea	1.24	293.13	*

Table 3

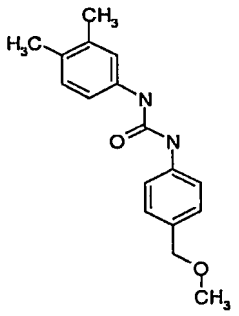
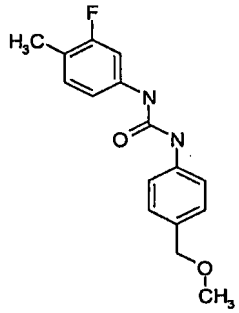
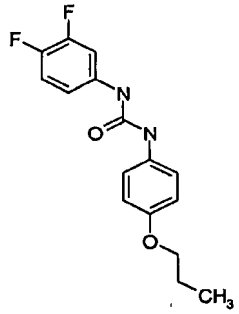
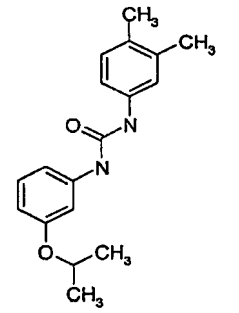
Compound	Name	R.T.	MS	IC50
684 	1-(3,4-dimethylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.22	285.18	*
685 	1-(3-fluoro-4-methylphenyl)-3-[4-(methoxymethyl)phenyl]urea	1.21	289.16	*
686 	1-(3,4-difluorophenyl)-3-(4-propoxyphenyl)urea	1.26	307.15	*
687 	1-(3,4-dimethylphenyl)-3-(3-isopropoxyphenyl)urea	1.27	299.2	*

Table 3

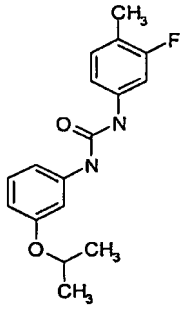
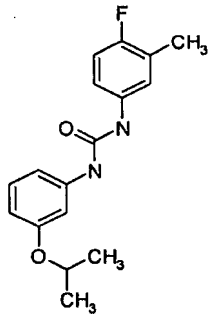
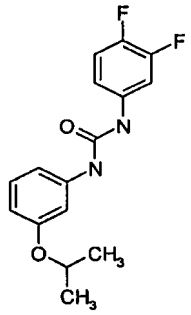
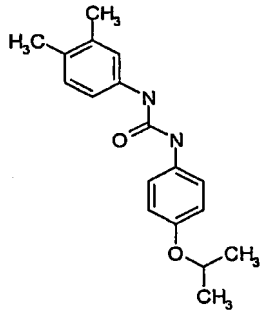
Compound	Name	R.T.	MS	IC50
688 	1-(3-fluoro-4-methylphenyl)-3-(3-isopropoxyphenyl)urea	1.27	303.17	*
689 	1-(4-fluoro-3-methylphenyl)-3-(3-isopropoxyphenyl)urea	1.26	303.17	*
690 	1-(3,4-difluorophenyl)-3-(3-isopropoxyphenyl)urea	1.25	307.15	*
691 	1-(3,4-dimethylphenyl)-3-(4-isopropoxyphenyl)urea	1.26	299.19	*

Table 3

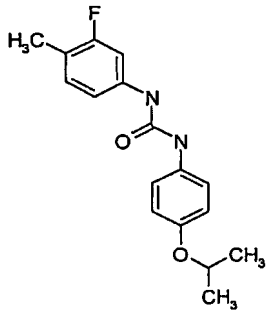
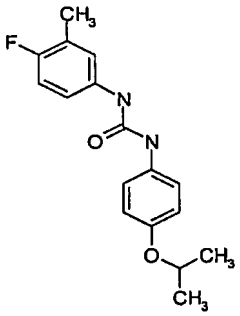
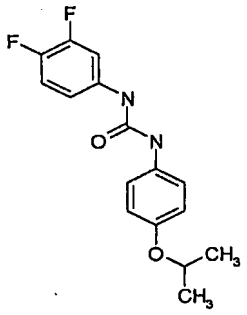
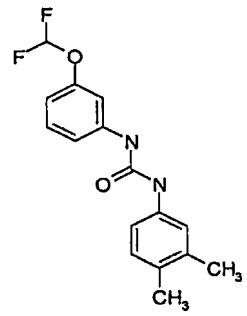
Compound	Name	R.T.	MS	IC50
692 	1-(3-fluoro-4-methylphenyl)-3-(4-isopropoxyphenyl)urea	1.25	303.17	*
693 	1-(4-fluoro-3-methylphenyl)-3-(4-isopropoxyphenyl)urea	1.24	303.17	*
694 	1-(3,4-difluorophenyl)-3-(4-isopropoxyphenyl)urea	1.24	307.15	*
695 	1-[3-(difluoromethoxy)phenyl]-3-(3,4-dimethylphenyl)urea	1.24	307.15	*

Table 3

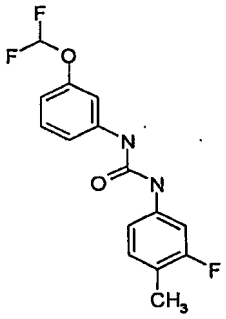
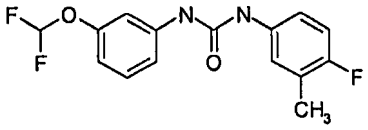
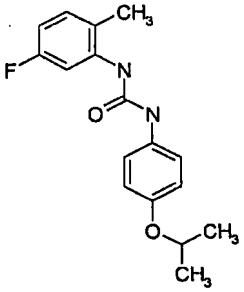
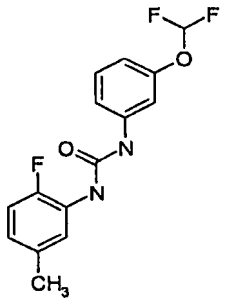
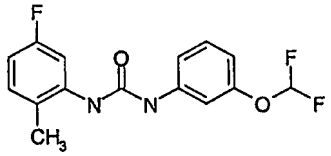
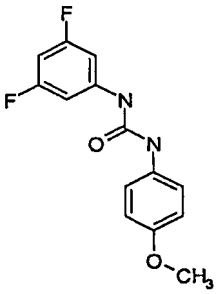
Compound	Name	R.T.	MS	IC50
696 	1-[3-(difluoromethoxy)phenyl]-3-(3-fluoro-4-methylphenyl)urea	1.24	311.13	*
697 	1-[3-(difluoromethoxy)phenyl]-3-(4-fluoro-3-methylphenyl)urea	1.23	311.13	*
698 	1-(5-fluoro-2-methylphenyl)-3-(4-isopropoxyphenyl)urea	1.25	303.17	*
699 	1-[3-(difluoromethoxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea	1.24	311.11	*
700 	1-[3-(difluoromethoxy)phenyl]-3-(5-fluoro-2-methylphenyl)urea	1.23	311.11	*
701 	1-(3,5-difluorophenyl)-3-(4-methoxyphenyl)urea	1.2	279.11	*

Table 3

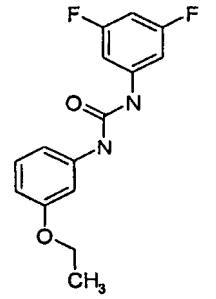
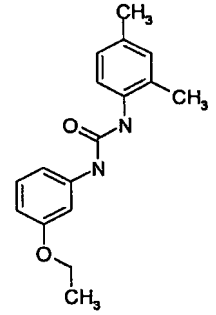
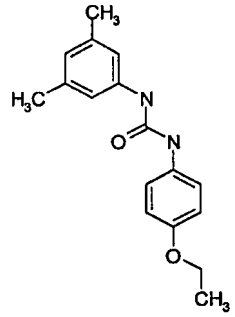
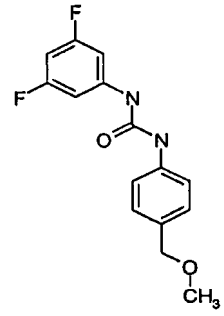
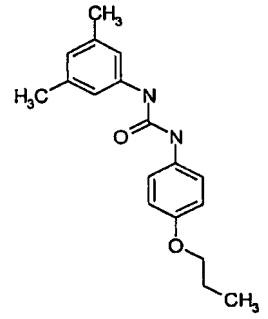
Compound	Name	R.T.	MS	IC50
702 	1-(3,5-difluorophenyl)-3-(3-ethoxyphenyl)urea	1.26	293.13	*
703 	1-(2,4-dimethylphenyl)-3-(3-ethoxyphenyl)urea	1.24	285.17	*
704 	1-(3,5-dimethylphenyl)-3-(4-ethoxyphenyl)urea	1.25	285.17	*
705 	1-(3,5-difluorophenyl)-3-[4-(methoxymethyl)phenyl]urea	1.21	293.13	*
706 	1-(3,5-dimethylphenyl)-3-(4-propoxyphenyl)urea	1.28	299.19	*

Table 3

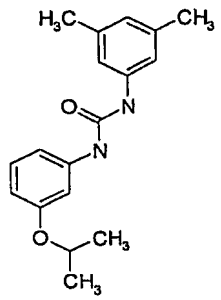
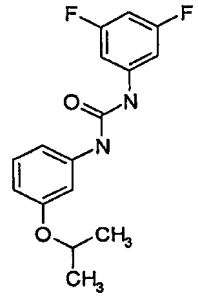
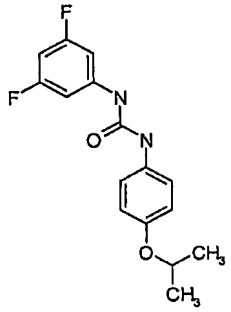
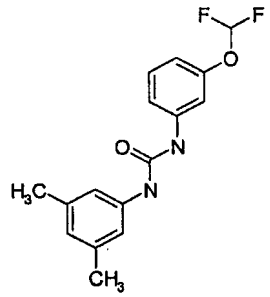
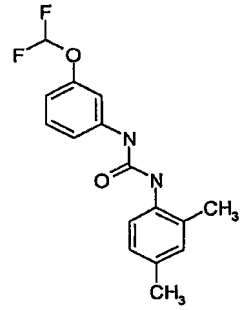
Compound	Name	R.T.	MS	IC50
707 	1-(3,5-dimethylphenyl)-3-(3-isopropoxyphenyl)urea	1.28	299.19	*
708 	1-(3,5-difluorophenyl)-3-(3-isopropoxyphenyl)urea	1.27	307.14	*
709 	1-(3,5-difluorophenyl)-3-(4-isopropoxyphenyl)urea	1.25	307.14	*
710 	1-[3-(difluoromethoxy)phenyl]-3-(3,5-dimethylphenyl)urea	1.25	307.14	*
711 	1-[3-(difluoromethoxy)phenyl]-3-(2,4-dimethylphenyl)urea	1.23	307.14	*

Table 3

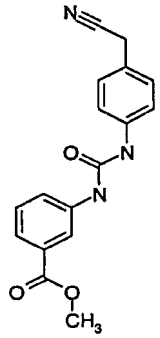
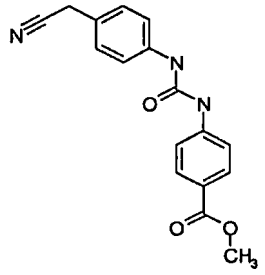
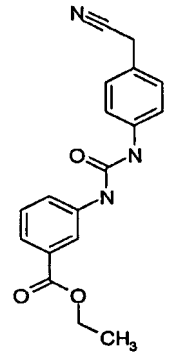
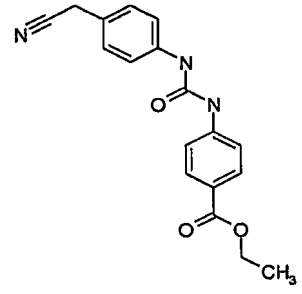
Compound	Name	R.T.	MS	IC50
712 	methyl 3-[({[4-(cyanomethyl)phenyl]amino}carbonyl)amino]benzoate	1.22	310.12	*
713 	methyl 4-[({[4-(cyanomethyl)phenyl]amino}carbonyl)amino]benzoate	1.23	310.12	*
714 	ethyl 3-[({[4-(cyanomethyl)phenyl]amino}carbonyl)amino]benzoate	1.25	324.13	*
715 	ethyl 4-[({[4-(cyanomethyl)phenyl]amino}carbonyl)amino]benzoate	1.26	324.13	*

Table 3

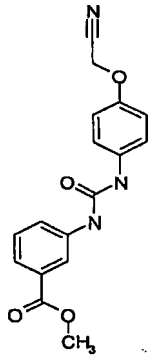
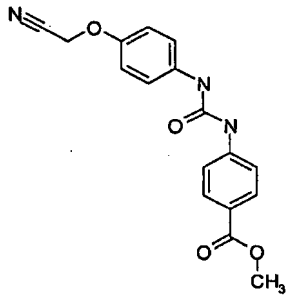
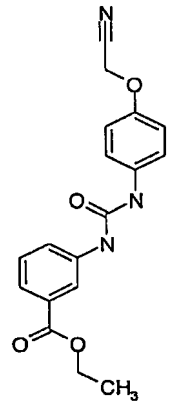
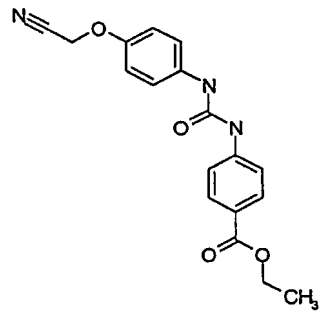
Compound	Name	R.T.	MS	IC50
716 	methyl 3-[({[4-(cyanomethoxy)phenyl]amino} carbonyl)amino]benzoate	1.22	326.12	*
717 	methyl 4-[({[4-(cyanomethoxy)phenyl]amino} carbonyl)amino]benzoate	1.23	326.13	*
718 	ethyl 3-[({[4-(cyanomethoxy)phenyl]amino} carbonyl)amino]benzoate	1.25	340.13	*
719 	ethyl 4-[({[4-(cyanomethoxy)phenyl]amino} carbonyl)amino]benzoate	1.25	340.14	*

Table 3

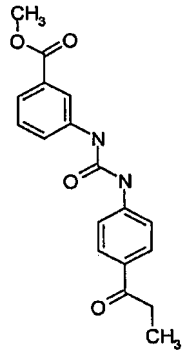
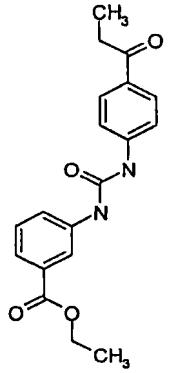
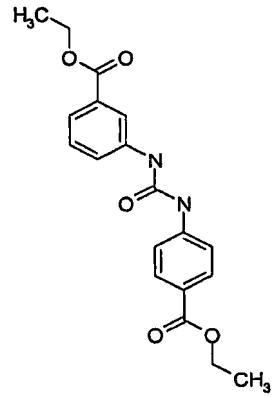
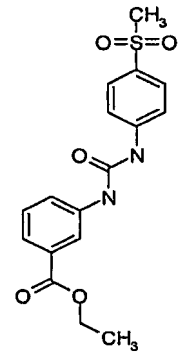
Compound	Name	R.T.	MS	IC50
720 	methyl 3-({[(4-propionylphenyl)amino]carbonyl}amino)benzoate	1.29	327.14	*
721 	ethyl 3-({[(4-propionylphenyl)amino]carbonyl}amino)benzoate	1.31	341.15	*
722 	ethyl 3-[({[4-(ethoxycarbonyl)phenyl]amino}carbonyl)amino]benzoate	1.34	357.15	*
723 	ethyl 3-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino]benzoate	1.24	363.12	*

Table 3

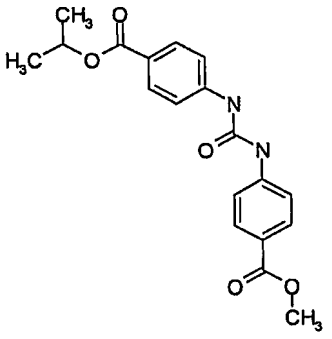
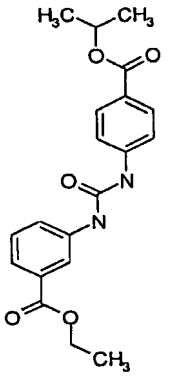
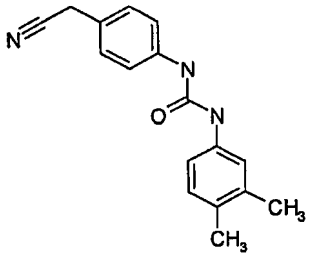
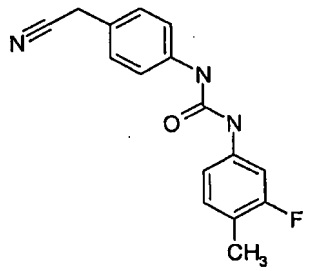
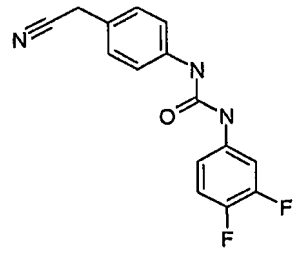
Compound	Name	R.T.	MS	IC50
724 	isopropyl methyl 4,4'-(carbonyldiimino)dibenzoate	1.35	357.14	*
725 	ethyl 3-[({[4-(isopropoxycarbonyl)phenyl]amino}carbonyl)amino]benzoate	1.36	371.16	*
726 	1-[4-(cyanomethyl)phenyl]-3-(3,4-dimethylphenyl)urea	1.27	280.15	*
727 	1-[4-(cyanomethyl)phenyl]-3-(3-fluoro-4-methylphenyl)urea	1.26	284.14	*
728 	1-[4-(cyanomethyl)phenyl]-3-(3,4-difluorophenyl)urea	1.24	288.11	*

Table 3

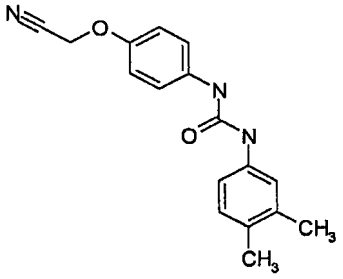
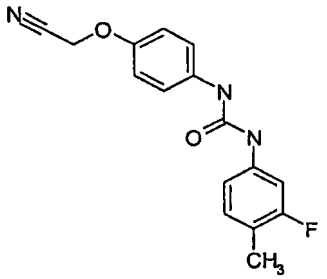
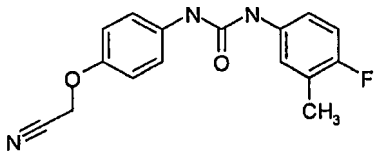
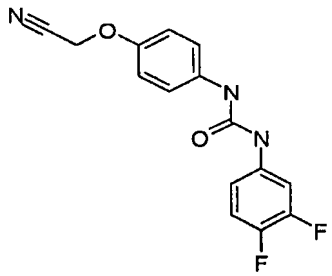
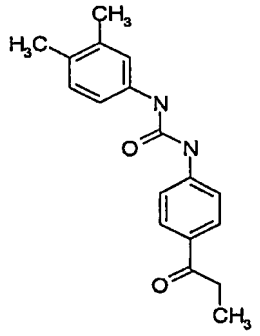
Compound	Name	R.T.	MS	IC50
729 	1-[4-(cyanomethoxy)phenyl]-3-(3,4-dimethylphenyl)urea	1.26	296.15	*
730 	1-[4-(cyanomethoxy)phenyl]-3-(3-fluoro-4-methylphenyl)urea	1.26	300.13	*
731 	1-[4-(cyanomethoxy)phenyl]-3-(4-fluoro-3-methylphenyl)urea	1.25	300.13	*
732 	1-[4-(cyanomethoxy)phenyl]-3-(3,4-difluorophenyl)urea	1.24	304.1	*
733 	1-(3,4-dimethylphenyl)-3-(4-propionylphenyl)urea	1.32	297.16	*

Table 3

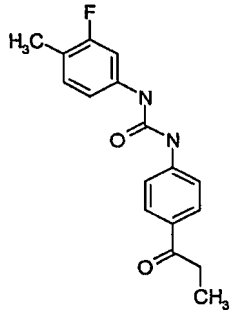
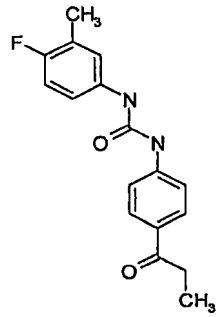
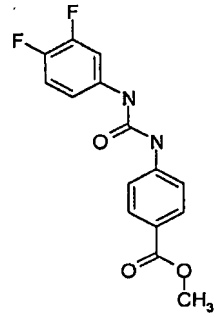
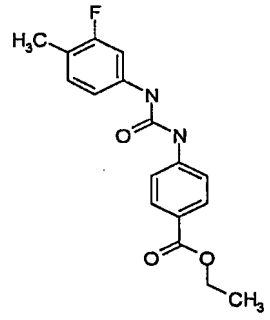
Compound	Name	R.T.	MS	IC50
734 	1-(3-fluoro-4-methylphenyl)-3-(4-propionylphenyl)urea	1.32	301.14	*
735 	1-(4-fluoro-3-methylphenyl)-3-(4-propionylphenyl)urea	1.32	301.14	*
736 	methyl 4-({[(3,4-difluorophenyl)amino]carbonyl }amino)benzoate	1.31	307.11	
737 	ethyl 4-({[(3-fluoro-4-methylphenyl)amino]carbonyl} amino)benzoate	1.35	317.13	*

Table 3

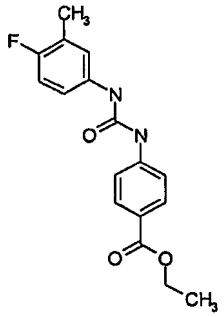
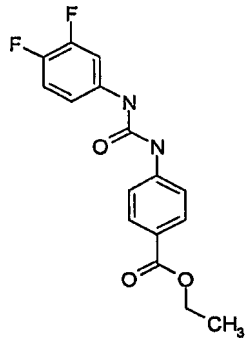
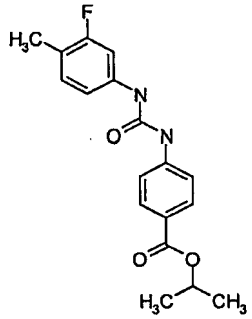
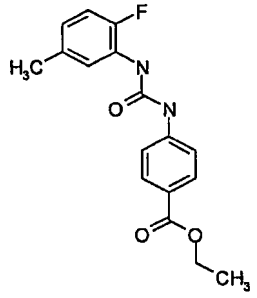
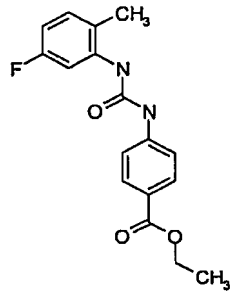
Compound	Name	R.T.	MS	IC50
738 	ethyl 4-({[(4-fluoro-3-methylphenyl)amino]carbonyl} amino)benzoate	1.33	317.14	*
739 	ethyl 4-({[(3,4-difluorophenyl)amino]carbonyl }amino)benzoate	1.34	321.12	*
740 	isopropyl 4-({[(3-fluoro-4-methylphenyl)amino]carbonyl} amino)benzoate	1.38	331.14	*
741 	ethyl 4-({[(2-fluoro-5-methylphenyl)amino]carbonyl} amino)benzoate	1.35	317.12	
742 	ethyl 4-({[(5-fluoro-2-methylphenyl)amino]carbonyl} amino)benzoate	1.34	317.12	

Table 3

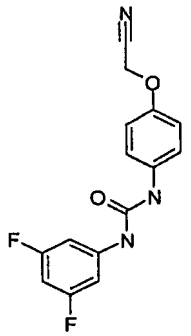
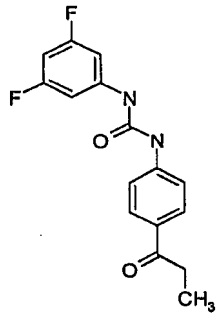
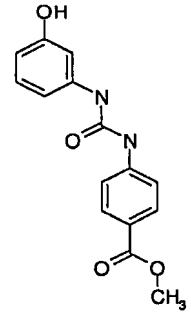
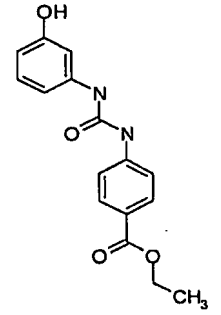
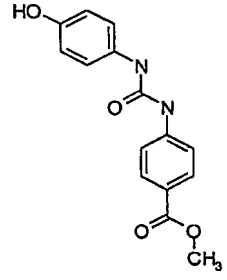
Compound	Name	R.T.	MS	IC50
743 	1-[4-(cyanomethoxy)phenyl]-3-(3,5-difluorophenyl)urea	1.26	304.1	*
744 	1-(3,5-difluorophenyl)-3-(4-propionylphenyl)urea	1.33	305.12	*
745 	methyl 4-({[(3-hydroxyphenyl)amino]carbonyl }amino)benzoate	1.2	287.11	*
746 	ethyl 4-({[(3-hydroxyphenyl)amino]carbonyl }amino)benzoate	1.24	301.12	*
747 	methyl 4-({[(4-hydroxyphenyl)amino]carbonyl }amino)benzoate	1.19	287.11	*

Table 3

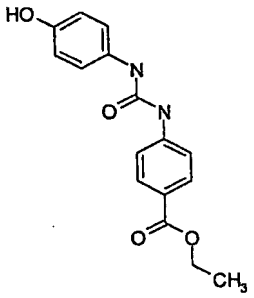
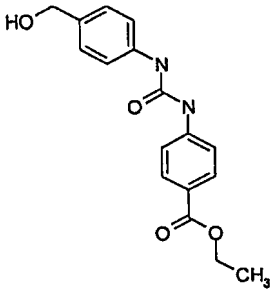
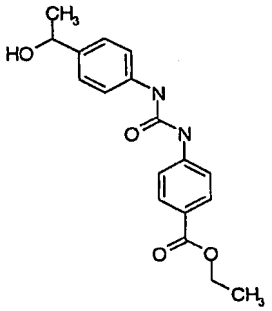
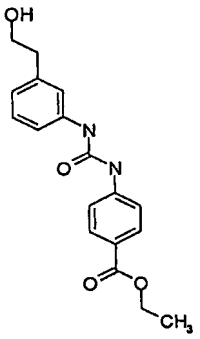
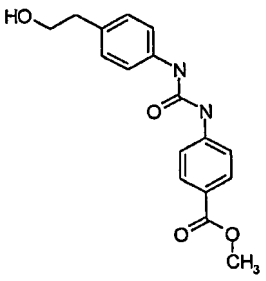
Compound	Name	R.T.	MS	IC50
748 	ethyl 4-({[(4-hydroxyphenyl)amino]carbonyl}amino)benzoate	1.23	301.12	*
749 	ethyl 4-[({[4-(hydroxymethyl)phenyl]amino}carbonyl)amino]benzoate	1.24	315.14	*
750 	ethyl 4-[({[4-(1-hydroxyethyl)phenyl]amino}carbonyl)amino]benzoate	1.26	329.15	*
751 	ethyl 4-[({[3-(2-hydroxyethyl)phenyl]amino}carbonyl)amino]benzoate	1.26	329.15	*
752 	methyl 4-[({[4-(2-hydroxyethyl)phenyl]amino}carbonyl)amino]benzoate	1.23	315.14	*

Table 3

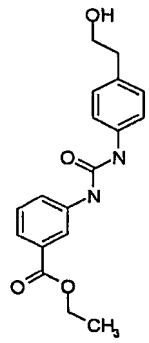
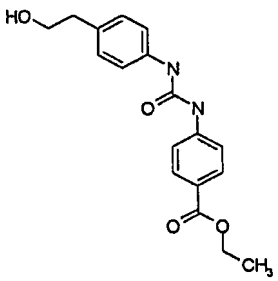
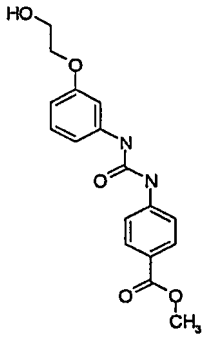
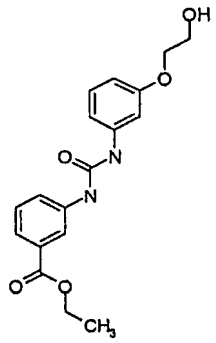
Compound	Name	R.T.	MS	IC50
753 	ethyl 3-[({[4-(2-hydroxyethyl)phenyl]amino}carbonyl)amino]benzoate	1.25	329.15	*
754 	ethyl 4-[({[4-(2-hydroxyethyl)phenyl]amino}carbonyl)amino]benzoate	1.26	329.15	*
755 	methyl 4-[({[3-(2-hydroxyethoxy)phenyl]amino}carbonyl)amino]benzoate	1.23	331.14	*
756 	ethyl 3-[({[3-(2-hydroxyethoxy)phenyl]amino}carbonyl)amino]benzoate	1.25	345.14	*

Table 3

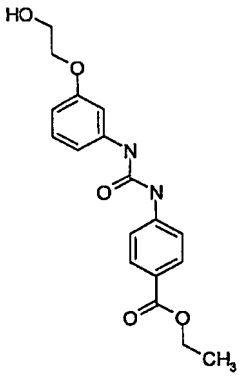
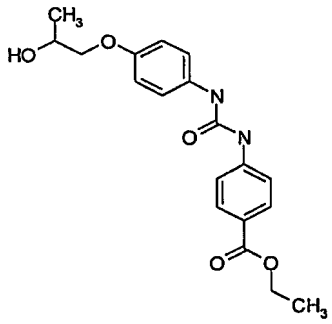
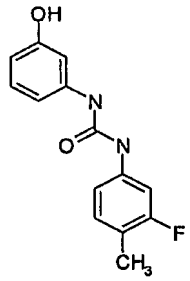
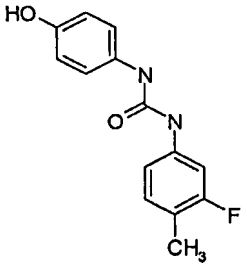
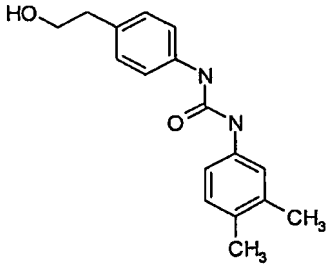
Compound	Name	R.T.	MS	IC50
757 	ethyl 4-[({[3-(2-hydroxyethoxy)phenyl]amino} carbonyl)amino]benzoate	1.26	345.15	*
758 	ethyl 4-[({[4-(2-hydroxypropoxy)phenyl]amino }carbonyl)amino]benzoate	1.26	359.16	*
759 	1-(3-fluoro-4-methylphenyl)-3-(3-hydroxyphenyl)urea	1.24	261.11	*
760 	1-(3-fluoro-4-methylphenyl)-3-(4-hydroxyphenyl)urea	1.23	261.11	*
761 	1-(3,4-dimethylphenyl)-3-[4-(2-hydroxyethyl)phenyl]urea	1.26	285.16	*

Table 3

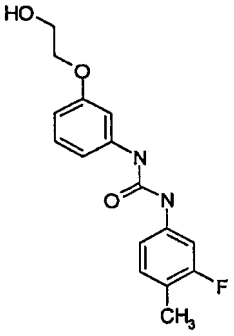
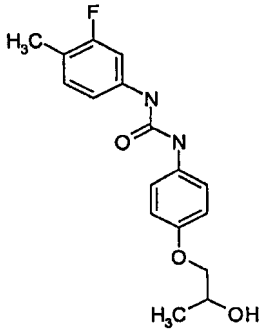
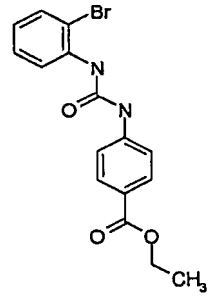
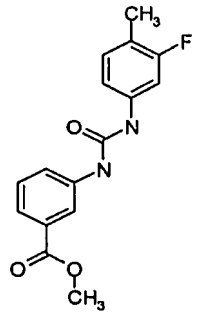
Compound	Name	R.T.	MS	IC50
762 	1-(3-fluoro-4-methylphenyl)-3-[3-(2-hydroxyethoxy)phenyl]urea	1.26	305.14	*
763 	1-(3-fluoro-4-methylphenyl)-3-[4-(2-hydroxypropoxy)phenyl]urea	1.26	319.15	*
764 	ethyl 4-({[(2-bromophenyl)amino]carbonyl}amino)benzoate			*
765 	methyl 3-({[(3-fluoro-4-methylphenyl)amino]carbonyl}amino)benzoate	1.31	303.14	*

Table 3

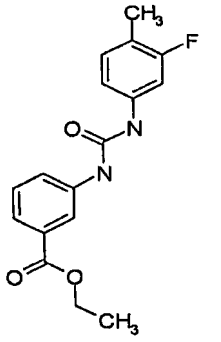
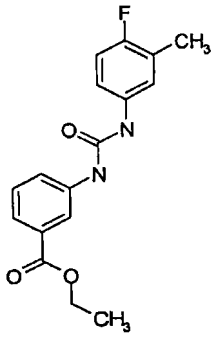
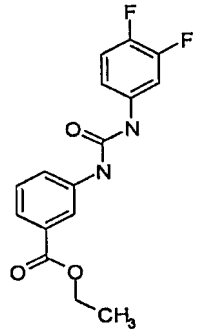
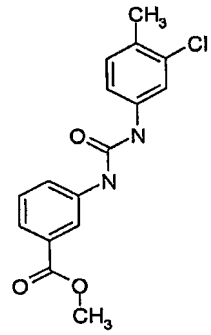
Compound	Name	R.T.	MS	IC50
766 	ethyl 3-({[(3-fluoro-4-methylphenyl)amino]carbonyl} amino)benzoate	1.34	317.14	*
767 	ethyl 3-({[(4-fluoro-3-methylphenyl)amino]carbonyl} amino)benzoate	1.33	317.14	*
768 	ethyl 3-({[(3,4-difluorophenyl)amino]carbonyl }amino)benzoate	1.32	321.12	*
769 	methyl 3-({[(3-chloro-4-methylphenyl)amino]carbonyl} amino)benzoate	1.35	319.12	*

Table 3

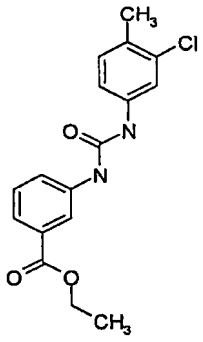
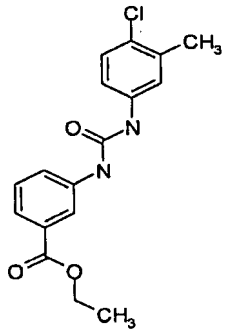
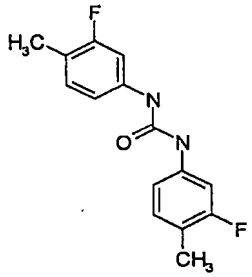
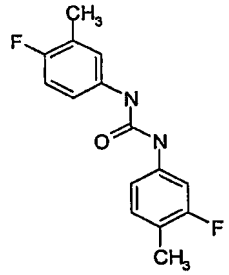
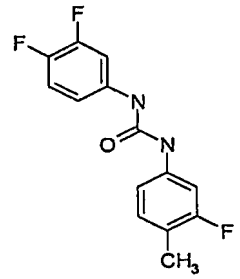
Compound	Name	R.T.	MS	IC50
770 	ethyl 3-({[(3-chloro-4-methylphenyl)amino]carbonyl} amino)benzoate	1.37	333.12	*
771 	ethyl 3-({[(4-chloro-3-methylphenyl)amino]carbonyl} amino)benzoate	1.37	333.13	*
772 	1,3-bis(3-fluoro-4-methylphenyl)urea	1.35	277.15	*
773 	1-(3-fluoro-4-methylphenyl)-3-(4-fluoro-3-methylphenyl)urea	1.33	277.14	
774 	1-(3,4-difluorophenyl)-3-(3-fluoro-4-methylphenyl)urea	1.33	281.12	*

Table 3

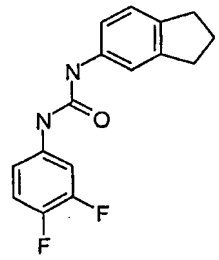
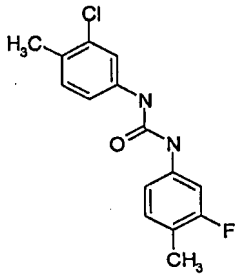
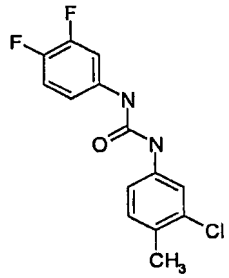
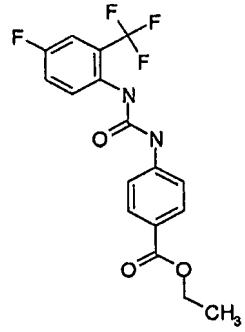
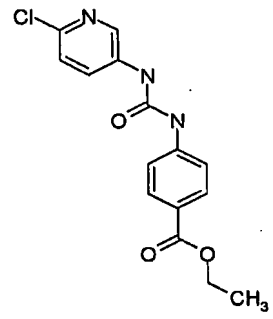
Compound	Name	R.T.	MS	IC50
775 	1-(3,4-difluorophenyl)-3-(2,3-dihydro-1H-inden-5-yl)urea	1.35	289.14	*
776 	1-(3-chloro-4-methylphenyl)-3-(3-fluoro-4-methylphenyl)urea	1.38	293.14	*
777 	1-(3-chloro-4-methylphenyl)-3-(3,4-difluorophenyl)urea	1.37	297.09	*
778 	ethyl 4-[({[4-fluoro-2-(trifluoromethyl)phenyl]amino}carbonyl)amino]benzoate	1.35	371.11	*
779 	ethyl 4-({[(6-chloropyridin-3-yl)amino]carbonyl}amino)benzoate	1.23	320.07	*

Table 3

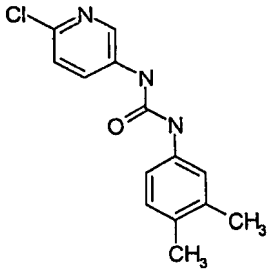
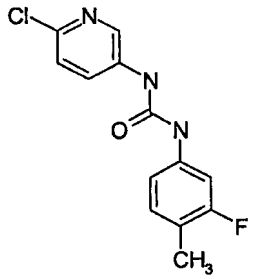
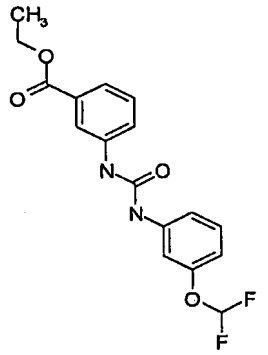
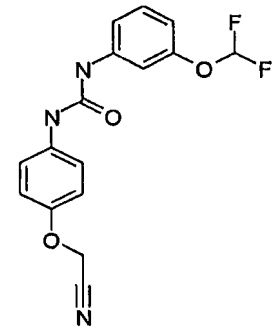
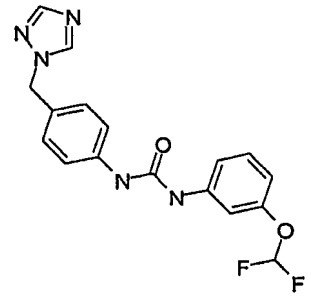
Compound	Name	R.T.	MS	IC50
780 	1-(6-chloropyridin-3-yl)-3-(3,4-dimethylphenyl)urea	1.23	276.08	*
781 	1-(6-chloropyridin-3-yl)-3-(3-fluoro-4-methylphenyl)urea	1.22	280.05	*
782 	ethyl 3-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate	1.3	351.15	*
783 	N-[4-(cyanomethoxy)phenyl]-N'-[3-(difluoromethoxy)phenyl]urea	1.15	334.21	*
784 	N-[3-(difluoromethoxy)phenyl]-N'-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]urea	1.14	360.18	*

Table 3

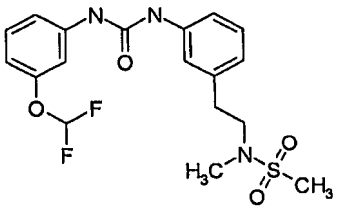
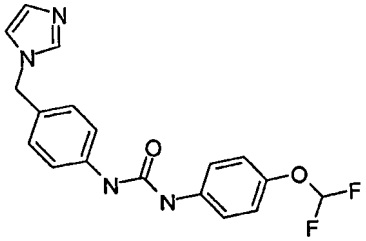
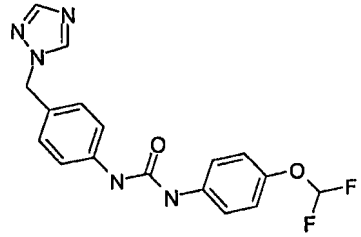
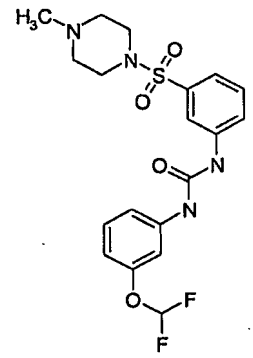
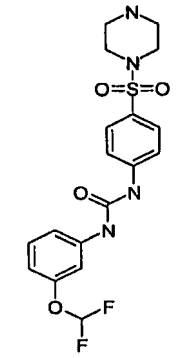
	Compound	Name	R.T.	MS	IC50
785		N-(2-{3-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]phenyl}ethyl)-N-methylmethanesulfonamide	1.17	414.19	*
786		N-[4-(difluoromethoxy)phenyl]-N'-[4-(1H-imidazol-1-ylmethyl)phenyl]urea	1.14	359.04	*
787		N-[4-(difluoromethoxy)phenyl]-N'-[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]urea	1.2	360.08	*
788		N-[3-(difluoromethoxy)phenyl]-N'-{3-[(4-methyl-1-piperazinyl)sulfonyl]phenyl}urea	1.17	441.08	*
789		N-[3-(difluoromethoxy)phenyl]-N'-[4-(1-piperazinylsulfonyl)phenyl]urea	1.18	427.09	*

Table 3

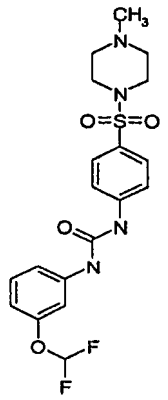
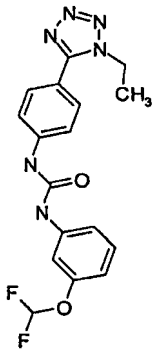
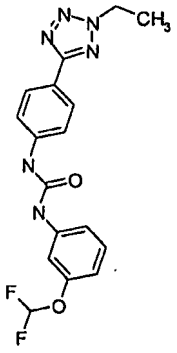
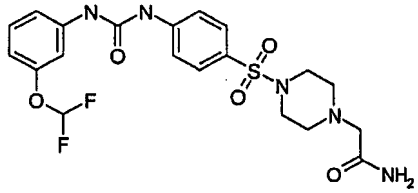
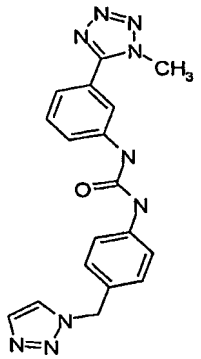
Compound	Name	R.T.	MS	IC50
790 	N-[3-(difluoromethoxy)phenyl]-N'-{4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl}urea	1.18	441.09	*
791 	N-[3-(difluoromethoxy)phenyl]-N'-[4-(1-ethyl-1H-tetrazol-5-yl)phenyl]urea	1.29	375.12	*
792 	N-[3-(difluoromethoxy)phenyl]-N'-[4-(2-ethyl-2H-tetrazol-5-yl)phenyl]urea	1.25	375.1	*
793 	2-[4-({4-[({[3-(difluoromethoxy)phenyl]amino}carbonyl)amino]phenyl}sulfonyl)-1-piperazinyl]acetamide	1.18	484.1	*

Table 3

Compound	Name	R.T.	MS	IC50
794 	N-[3-(1-methyl-1H-tetrazol-5-yl)phenyl]-N'-[4-(1H-1,2,3-triazol-1-ylmethyl)phenyl]urea	1.19	376.17	*

EXAMPLE 4. BACULOVIRAL PREPARATIONS FOR CB1 EXPRESSION

This Example illustrates the preparation of recombinant baculovirus for use in generating CB1-expressing insect cells.

The human CB1 sequence has GenBank Accession Number HSU73304, and was reported by Hoehe et al. (1991) *New Biol. 3(9)*:880-85. Human CB1 (hCB1) cDNA is amplified from a human brain cDNA library (Gibco BRL, Gaithersburg, MD) using PCR, in which the 5' primer includes the optimal Kozak sequence CCACC. The resulting PCR product is cloned into pcDNA3.1/V5-His-TOPO (Invitrogen Corp, Carlsbad, CA) using the multiple cloning site, and then subcloned into pBACPAK$_8$ (BD Biosciences, Palo Alto, CA) at the Bam/Xho site to yield a hCB1 baculoviral expression vector.

The hCB1 baculoviral expression vector is co-transfected along with BACULOGOLD DNA (BD PharMingen, San Diego, CA) into S*f*9 cells. The S*f*9 cell culture supernatant is harvested three days post-transfection. The recombinant virus-containing supernatant is serially diluted in Hink's TNM-FH insect medium (JRH Biosciences, Kansas City, MO) supplemented with Grace's salts and with 4.1mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques are selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) is used to infect a separate T25 flask containing 2 x 10^6 S*f*9 cells in 5 ml of insect medium. After five days of incubation at 27°C, supernatant medium is harvested from each of the T25 infections for use as passage 1 inoculum.

Two of seven recombinant baculoviral clones are then chosen for a second round of amplification, using 1 ml of passage 1 stock to infect 1 x 10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight hours post infection, passage 2 medium from each 100 ml preparation is harvested and plaque assayed for titer. The cell pellets from the second round of amplification are assayed by affinity binding as described below to verify recombinant receptor expression. A third round of amplification is then initiated using a multiplicity of infection of 0.1 to infect a liter of S*f*9 cells. Seventy-two hours post-infection the supernatant medium is harvested to yield passage 3 baculoviral stock.

The remaining cell pellet is assayed for affinity binding. Radioligand is 25pM-5.0nM [^{3}H]CP55,940 for saturation binding and 0.5nM for competition binding (New England Nuclear Corp., Boston, MA); the hCB1-expressing baculoviral cells are used; the assay buffer contains 50 mM Tris pH 7.4, 120mM NaCl, 5 mM $MgCl_2$, 0.5% BSA and 0.2 mg/ml bacitracin; filtration is carried out using GF/C WHATMAN filters (presoaked in 0.3% non-fat dry milk (H_2O) for 2 hours prior to use); and the filters are washed twice with 5 mL cold 50mM Tris pH.7.4.

Titer of the passage 3 baculoviral stock is determined by plaque assay and a multiplicity of infection, incubation time course, binding assay experiment is carried out to determine conditions for optimal receptor expression.

EXAMPLE 5. BACULOVIRAL INFECTIONS

Log-phase Sf9 cells (Invitrogen Corp., Carlsbad, CA), are infected with one or more stocks of recombinant baculovirus followed by culturing in insect medium at 27°C. Infections are carried out either only with virus directing the expression of hCB1 or with this virus in combination with three G-protein subunit-expression virus stocks: 1) rat $G\alpha_{i2}$ G-protein-encoding virus stock, 2) bovine β1 G-protein-encoding virus stock, and 3) human γ2 G-protein-encoding virus stock, all of which are obtained from Biosignal Inc., Montreal, Canada.

Typical hCB1 infections are conducted using Sf9 cells that are cultured in insect medium supplemented with 10% heat-inactivated fetal bovine serum (FBS) as discussed above. Higher receptor and G-protein (Gα, Gβ, Gγ) expression can be obtained if the Sf9 cells are cultured in insect medium with 5% FBS and 5% Gibco serum-free medium (Invitrogen Corp.; Carlsbad, CA). Maximal CB1 expression and functional activity is achieved if the Sf9 cells are cultured in insect medium without FBS and with 10% Gibco serum-free medium. The infections are carried out at a multiplicity of infection of 0.1:1.0:0.5:0.5. At 72 hours post-infection, a sample of cell suspension is analyzed for viability by trypan blue dye exclusion, and the remaining Sf9 cells are harvested via centrifugation (3000 rpm/ 10 min/ 4°C).

EXAMPLE 6. PURIFIED RECOMBINANT INSECT CELL MEMBRANES

Sf9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 μg/ml leupeptin, 2 μg/ml Aprotinin, 200 μM PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 min/ 4°C) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 X g/ 30 min, 4°C) and the resulting pellet resuspended in 30 ml homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots at -80°C until needed. The protein concentration of the resulting membrane preparation (hereinafter "P2 membranes") is measured using a Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 100-150 mg of total membrane protein.

EXAMPLE 7. RADIOLIGAND BINDING ASSAYS

P2 membranes are resuspended by Dounce homogenization (tight pestle) in binding buffer (50 mM Tris pH. 7.4, 120mM NaCl, 5 mM $MgCl_2$, 0.5% BSA and 0.2 mg/ml bacitracin).

For saturation binding analysis, membranes (10 μg) are added to polypropylene tubes containing 25pM–0.5nM [^{3}H]CP55,940 (New England Nuclear Corp., Boston, MA). Nonspecific binding is determined in the presence of 10μM CP55,940 (Tocris Cookson Inc., Ellisville, MO) and

accounted for less than 10% of total binding. For evaluation of guanine nucleotide effects on receptor affinity, GTPγS is added to duplicate tubes at the final concentration of 50 μM.

For competition analysis, membranes (10μg) are added to polypropylene tubes containing 0.5nM [^{3}H]CP55,940. Non-radiolabeled displacers are added to separate assays at concentrations ranging from 10^{-10} M to 10^{-5} M to yield a final volume of 0.250 mL. Nonspecific binding is determined in the presence of 10μM CP55,940 and accounted for less than 10% of total binding. Following a one-hour incubation at room temperature, the reaction is terminated by rapid vacuum filtration. Samples are filtered over presoaked (0.3% non-fat dry milk for 2 h prior to use) GF/C WHATMAN filters and rinsed 2 times with 5 mL cold 50mM Tris pH 7.4. Remaining bound radioactivity is quantified by gamma counting. K_i and Hill coefficient ("nH") are determined by fitting the Hill equation to the measured values with the aid of SIGMAPLOT software (SPSS Inc., Chicago, IL).

EXAMPLE 8. AGONIST-INDUCED GTP BINDING

This Example illustrates the use of agonist-stimulated GTPγ^{35}S binding ("GTP binding") activity to identify CB1 agonists and antagonists, and to differentiate neutral antagonists from those that possess inverse agonist activity. This assay can also be used to detect partial agonism mediated by antagonist compounds. A compound being analyzed in this assay is referred to herein as a "test compound." Agonist-stimulated GTP binding activity is measured as follows: Four independent baculoviral stocks (one directing the expression of hCB1 and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of *Sf*9 cells as described in Example 5.

Agonist-stimulated GTP binding on purified membranes (as described in Example 6) is initially assessed using the cannabinoid agonist CP55,940 to ascertain that the receptor/G-protein-alpha-beta-gamma combination(s) yield a functional response as measured by GTP binding.

P2 membranes are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM $MgCl_2$, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 10 μg protein/reaction tube. After adding increasing doses of the agonist CP55,940 at concentrations ranging from 10^{-12} M to 10^{-6} M, reactions are initiated by the addition of 100 pM GTPγ^{35}S. In competition experiments, non-radiolabeled test compounds are added to separate assays at concentrations ranging from 10^{-10} M to 10^{-5} M along with 1 nM CP55,940 to yield a final volume of 0.25 mL.

Following a 60-minute incubation at room temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound) GTPγ^{35}S is determined by measuring the bound radioactivity, preferably

by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTPγ^{35}S and typically represents less than 5 percent of total binding. Data is expressed as percent above basal (baseline). The results of these GTP binding experiments are analyzed using SIGMAPLOT software and IC_{50} determined. The IC_{50} may then be used to generate K_i as described by Cheng and Prusoff (1973) *Biochem Pharmacol. 22(23)*:3099-108.

Neutral antagonists are those test compounds that reduce the CP55,940-stimulated GTP binding activity towards, but not below, baseline (the level of GTP bound by membranes in this assay in the absence of added CP55,940 or other agonist and in the further absence of any test compound).

In contrast, in the absence of added CP55,940, CB1 inverse agonists reduce the GTP binding activity of the receptor-containing membranes below baseline. If a test compound that displays antagonist activity does not reduce the GTP binding activity below baseline in the absence of the CB1 agonist, it is characterized as a neutral antagonist.

An antagonist test compound that elevates GTP binding activity above baseline in the absence of added CP55,940 in this GTP binding assay is characterized as having partial agonist activity. Preferred CB1 antagonists do not elevate GTP binding activity under such conditions more than 10%, more preferably less than 5% and most preferably less than 2% of the maximal response elicited by the agonist, CP55,940.

The GTP binding assay can also be used to determine antagonist selectivity towards CB1 over CB2. Agonist-stimulated GTP binding activity at CB2 is measured as described above for CB1 except that the *Sf*9 cells are infected with one baculoviral stock directing the expression of hCB2 and three directing the expression of each of the three subunits of a heterotrimeric G-protein. The IC_{50} and K_i are generated as described above for CB1.

EXAMPLE 9. SURMOUNTABILITY ASSAYS

Certain CB1 antagonists are insurmountable with regard to the agonist induced GTPγ^{35}S binding effect. To assess surmountability, P2 membranes are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.4, 120 mM NaCl, 5 mM $MgCl_2$, 2 mM EGTA, 10μg/ml saponin, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 10 μg protein/reaction tube. Agonist dose-response curves (typically CP55,940) at concentrations ranging from 10^{-12} M to 10^{-5} M, are run either in the absence or in the presence of a test compound at one of several doses up to 100X the IC_{50} of the test compound as measured in the competition GTPγ^{35}S binding. The reactions are initiated by the addition of 100 pM GTPγ^{35}S to yield a final volume of 0.25 mL. Following a 90-minute incubation at room temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound)

GTPγ^{35}S is determined by measuring the bound radioactivity, preferably by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 μM GTPγS and typically represents less than 5 percent of total binding. Data is expressed as percent above basal (baseline). The results of these GTP binding experiments may be conveniently analyzed using SIGMAPLOT software. A surmountable test compound is one which shifts the EC_{50} of the agonist to the right (weaker) without affecting the maximum functional response of the agonist. Insurmountable antagonist test compounds have no significant effect on the hCB1 agonist EC_{50} at concentrations roughly 100X the IC_{50}, but significantly reduce or eliminate the agonist stimulated GTPγ^{35}S binding response of the receptor.

EXAMPLE 10. MDCK CYTOTOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μL of test compound is added to each well of a clear bottom 96-well plate (Packard, Meriden, CT) to give final concentration of compound in the assay of 10 μM, 100 μM or 200 μM. Solvent without test compound is added to control wells.

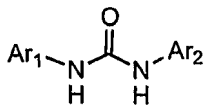
MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1 x 10^6 cells/mL with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μL of diluted cells is added to each well, except for five standard curve control wells that contain 100 μL of warm medium without cells. The plate is then incubated at 37°C under 95% O_2, 5% CO_2 for 2 h with constant shaking. After incubation, 50 μL of mammalian cell lysis solution (from the Packard (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 min.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM, and 12.5 nM. PACKARD substrate solution (50 μL) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 min. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by

wrapping plates in foil and placing in the dark for 10 min. Luminescence is then measured at 22°C using a luminescence counter (*e.g.*, PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μM of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μM concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

What is claimed is:

1. A method for treating a condition responsive to CB1 modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 and Ar_2 are independently chosen from phenyl and 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(a) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(b) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

M is absent, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, $S(O)_m$, $N(R_z)$, $C(=O)N(R_z)$, $C(=NH)N(R_z)$, $N(R_z)C(=O)$, $N(R_z)C(=NH)$, $N(R_z)C(=O)O$, $OC(=O)N(R_z)$, $N(R_z)S(O)_m$, $S(O)_mN(R_z)$ and $N[S(O)_mR_z]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(c) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl.

2. A method according to claim 1, wherein Ar_1 and Ar_2 are independently phenyl, pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently located *meta* or *para* to the point of attachment, wherein each substituent is independently:

(a) halogen, hydroxy or cyano; or

(b) C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_4alkanoyl, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl or a 5- or 6-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, and C_1-C_4haloalkyl.

3. A method according to claim 1 or claim 2, wherein Ar_1 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy.

4. A method according to claim 3, wherein Ar_1 is phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl or 4-(C_1-C_4alkoxy)-phenyl.

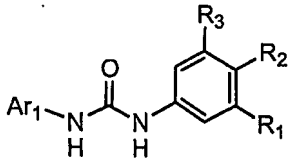
5. A method according to any one of claims 1-4, wherein Ar_2 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle.

6. A method according to claim 5, wherein Ar_2 is phenyl that is substituted with exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

7. A method according to claim 5, wherein Ar_2 is phenyl that is substituted with exactly one substituent chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

8. A method according to claim 7, wherein Ar_2 is phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-cyano-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-cyano-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl or 4-(C_1-C_4alkoxy)-phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl or 4-acetyl-phenyl.

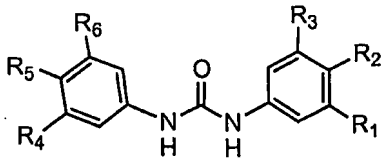
9. A method according to claim 1, wherein the compound has the formula:



wherein R_1, R_2 and R_3 are independently chosen from hydrogen and R_x, and wherein at least one of R_1 and R_2 is not hydrogen.

10. A method according to claim 9, wherein R_1, R_2 and R_3 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl and 5- and 6-membered heterocycles.

11. A method according to claim 9, wherein the compound has the formula:



wherein R_4, R_5 and R_6 are independently chosen from hydrogen and R_x, and wherein at least one of R_4 and R_5 is not hydrogen.

12. A method according to claim 11, wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

13. A method according to claim 1, wherein the compound is:
ethyl 3-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate;
methyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]-2-methoxybenzoate;
methyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate;
N-(1-bromoisoquinolin-3-yl)-N'-(4-methylphenyl)urea;
N-(2,3-dihydro-1H-inden-5-yl)-N'-phenylurea;
N-(2,4-dimethylphenyl)-N'-(4-ethylphenyl)urea;
N-(2,5-dimethylphenyl)-N'-(4-ethylphenyl)urea;
N-(2-amino-5-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(2-chloropyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3,4-dichlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3,5-dichlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-acetylphenyl)-N'-(3-isopropoxyphenyl)urea;
N-(3-acetylphenyl)-N'-(4-ethoxyphenyl)urea;
N-(3-acetylphenyl)-N'-(4-ethylphenyl)urea;
N-(3-acetylphenyl)-N'-(4-isopropoxyphenyl)urea;
N-(3-acetylphenyl)-N'-(4-isopropylphenyl)urea;
N-(3-acetylphenyl)-N'-(4-propoxyphenyl)urea;
N-(3-acetylphenyl)-N'-(4-propylphenyl)urea;
N-(3-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(3-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-acetylphenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(3-chloro-4-morpholin-4-ylphenyl)-N'-(3-methylphenyl)urea;
N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-chlorophenyl)-N'-(3-ethoxyphenyl)urea;
N-(3-chlorophenyl)-N'-(3-isopropoxyphenyl)urea;

N-(3-chlorophenyl)-N'-(4-ethoxyphenyl)urea;
N-(3-chlorophenyl)-N'-(4-ethylphenyl)urea;
N-(3-chlorophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(3-chlorophenyl)-N'-(4-propoxyphenyl)urea;
N-(3-chlorophenyl)-N'-(4-propylphenyl)urea;
N-(3-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(3-chlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-chlorophenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(3-cyano-4-fluorophenyl)-N'-(4-ethylphenyl)urea;
N-(3-cyano-4-fluorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-cyanophenyl)-N'-(3-ethoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(3-isopropoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(4-ethoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(4-ethylphenyl)urea;
N-(3-cyanophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(4-isopropylphenyl)urea;
N-(3-cyanophenyl)-N'-(4-methoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(4-methylphenyl)urea;
N-(3-cyanophenyl)-N'-(4-propoxyphenyl)urea;
N-(3-cyanophenyl)-N'-(4-propylphenyl)urea;
N-(3-cyanophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(3-cyanophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-cyanophenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-ethoxyphenyl)-N'-(3-ethylphenyl)urea;
N-(3-ethoxyphenyl)-N'-(3-fluorophenyl)urea;
N-(3-ethoxyphenyl)-N'-(4-ethylphenyl)urea;
N-(3-ethoxyphenyl)-N'-(4-fluorophenyl)urea;
N-(3-ethoxyphenyl)-N'-(4-methylphenyl)urea;
N-(3-ethoxyphenyl)-N'-phenylurea;
N-(3-ethylphenyl)-N'-(3-isopropoxyphenyl)urea;
N-(3-ethylphenyl)-N'-(4-ethylphenyl)urea;
N-(3-ethylphenyl)-N'-(4-isopropoxyphenyl)urea;
N-(3-ethylphenyl)-N'-(4-methylphenyl)urea;
N-(3-ethylphenyl)-N'-(4-propoxyphenyl)urea;
N-(3-ethylphenyl)-N'-(4-propylphenyl)urea;
N-(3-ethylphenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(3-fluoro-4-methylphenyl)-N'-(4-methylphenyl)urea;

N-(3-fluorophenyl)-N'-(3-isopropoxyphenyl)urea;
N-(3-fluorophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(3-fluorophenyl)-N'-(4-methylphenyl)urea;
N-(3-fluorophenyl)-N'-(4-propoxyphenyl)urea;
N-(3-fluorophenyl)-N'-(4-propylphenyl)urea;
N-(3-fluorophenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(3-isopropoxyphenyl)-N'-(3-methylphenyl)urea;
N-(3-isopropoxyphenyl)-N'-(4-methylphenyl)urea;
N-(3-isopropoxyphenyl)-N'-phenylurea;
N-(3-methylphenyl)-N'-(4-piperidin-1-ylphenyl)urea;
N-(3-methylphenyl)-N'-(4-propoxyphenyl)urea;
N-(3-methylphenyl)-N'-(4-propylphenyl)urea;
N-(3-methylphenyl)-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea;
N-(3-methylphenyl)-N'-phenylurea;
N-(4-acetylphenyl)-N'-(3-bromophenyl)urea;
N-(4-acetylphenyl)-N'-(3-chlorophenyl)urea;
N-(4-acetylphenyl)-N'-(3-ethoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(3-ethylphenyl)urea;
N-(4-acetylphenyl)-N'-(3-fluorophenyl)urea;
N-(4-acetylphenyl)-N'-(3-isopropoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(3-methoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(4-chlorophenyl)urea;
N-(4-acetylphenyl)-N'-(4-ethoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(4-ethylphenyl)urea;
N-(4-acetylphenyl)-N'-(4-fluorophenyl)urea;
N-(4-acetylphenyl)-N'-(4-isopropoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(4-isopropylphenyl)urea;
N-(4-acetylphenyl)-N'-(4-methoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(4-methylphenyl)urea;
N-(4-acetylphenyl)-N'-(4-propoxyphenyl)urea;
N-(4-acetylphenyl)-N'-(4-propylphenyl)urea;
N-(4-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(4-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(4-acetylphenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(4-benzoylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(4-butylphenyl)-N'-(3-methylphenyl)urea;
N-(4-butylphenyl)-N'-(4-ethylphenyl)urea;
N-(4-butylphenyl)-N'-(4-methylphenyl)urea;

N-(4-butylphenyl)-N'-phenylurea;
N-(4-chloro-2-methylphenyl)-N'-(4-ethylphenyl)urea;
N-(4-chlorophenyl)-N'-(3-ethoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(3-isopropoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(4-ethoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(4-ethylphenyl)urea;
N-(4-chlorophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(4-isopropylphenyl)urea;
N-(4-chlorophenyl)-N'-(4-methoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(4-methylphenyl)urea;
N-(4-chlorophenyl)-N'-(4-propoxyphenyl)urea;
N-(4-chlorophenyl)-N'-(4-propylphenyl)urea;
N-(4-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(4-chlorophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(4-chlorophenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(4-chlorophenyl)-N'-phenylurea;
N-(4-cyanophenyl)-N'-(3-ethoxyphenyl)urea;
N-(4-cyanophenyl)-N'-(4-ethoxyphenyl)urea;
N-(4-cyanophenyl)-N'-(4-ethylphenyl)urea;
N-(4-cyanophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(4-cyanophenyl)-N'-(4-isopropylphenyl)urea;
N-(4-cyanophenyl)-N'-(4-propoxyphenyl)urea;
N-(4-cyanophenyl)-N'-(4-propylphenyl)urea;
N-(4-cyanophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(4-cyanophenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(4-cyanophenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(4-ethoxyphenyl)-N'-(3-ethylphenyl)urea;
N-(4-ethoxyphenyl)-N'-(3-fluorophenyl)urea;
N-(4-ethoxyphenyl)-N'-(3-methylphenyl)urea;
N-(4-ethoxyphenyl)-N'-(4-ethylphenyl)urea;
N-(4-ethoxyphenyl)-N'-(4-fluorophenyl)urea;
N-(4-ethoxyphenyl)-N'-phenylurea;
N-(4-ethylphenyl)-N'-(2-fluoro-4-methylphenyl)urea;
N-(4-ethylphenyl)-N'-(2-fluoro-5-methylphenyl)urea;
N-(4-ethylphenyl)-N'-(3-fluorophenyl)urea;
N-(4-ethylphenyl)-N'-(3-isopropoxyphenyl)urea;
N-(4-ethylphenyl)-N'-(3-methoxyphenyl)urea;
N-(4-ethylphenyl)-N'-(3-methylphenyl)urea;

N-(4-ethylphenyl)-N'-(4-fluorophenyl)urea;
N-(4-ethylphenyl)-N'-(4-hydroxyphenyl)urea;
N-(4-ethylphenyl)-N'-(4-iodophenyl)urea;
N-(4-ethylphenyl)-N'-(4-isopropoxyphenyl)urea;
N-(4-ethylphenyl)-N'-(4-isopropylphenyl)urea;
N-(4-ethylphenyl)-N'-(4-methoxyphenyl)urea;
N-(4-ethylphenyl)-N'-(4-methylphenyl)urea;
N-(4-ethylphenyl)-N'-(4-propoxyphenyl)urea;
N-(4-ethylphenyl)-N'-(4-propylphenyl)urea;
N-(4-ethylphenyl)-N'-[3-(hydroxymethyl)phenyl]urea;
N-(4-ethylphenyl)-N'-[3-(methoxymethyl)phenyl]urea;
N-(4-ethylphenyl)-N'-[4-(hydroxymethyl)phenyl]urea;
N-(4-ethylphenyl)-N'-[4-(methoxymethyl)phenyl]urea;
N-(4-ethylphenyl)-N'-phenylurea;
N-(4-ethylphenyl)-N'-quinolin-3-ylurea;
N-(4-ethylphenyl)-N'-quinolin-6-ylurea;
N-(4-fluorophenyl)-N'-(3-isopropoxyphenyl)urea;
N-(4-fluorophenyl)-N'-(4-isopropoxyphenyl)urea;
N-(4-fluorophenyl)-N'-(4-isopropylphenyl)urea;
N-(4-fluorophenyl)-N'-(4-methylphenyl)urea;
N-(4-fluorophenyl)-N'-(4-propoxyphenyl)urea;
N-(4-fluorophenyl)-N'-(4-propylphenyl)urea;
N-(4-isopropoxyphenyl)-N'-(3-methylphenyl)urea;
N-(4-isopropoxyphenyl)-N'-(4-methylphenyl)urea;
N-(4-isopropoxyphenyl)-N'-phenylurea;
N-(4-isopropylphenyl)-N'-(4-methylphenyl)urea;
N-(4-isopropylphenyl)-N'-phenylurea;
N-(4-methylphenyl)-N'-(4-piperidin-1-ylphenyl)urea;
N-(4-methylphenyl)-N'-(4-propoxyphenyl)urea;
N-(4-methylphenyl)-N'-(4-propylphenyl)urea;
N-(4-methylphenyl)-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea;
N-(4-methylphenyl)-N'-phenylurea;
N-(5-chloropyridin-2-yl)-N'-(4-ethylphenyl)urea;
N-(6-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(6-chloropyridin-3-yl)-N'-(4-ethylphenyl)urea;
N-(6-chloropyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(8-chloro-1-naphthyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N,N'-bis(4-ethylphenyl)urea;

N,N'-bis(4-methylphenyl)urea;

N,N'-bis[3-(difluoromethoxy)phenyl]urea;

N,N'-bis[4-(difluoromethoxy)-3-methoxyphenyl]urea;

N,N'-bis[4-(difluoromethoxy)phenyl]urea;

N-[3-(2-hydroxyethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;

N-[3-(5-chloropyridin-2-yl)phenyl]-N'-(4-ethylphenyl)urea;

N-[3-(5-chloropyridin-2-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[3-(5-cyanopyridin-3-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[3-(6-chloro-5-methoxypyridin-2-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[3-(cyclopentyloxy)-4-methoxyphenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[3-(difluoromethoxy)phenyl]-N'-(2-ethylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(2-methylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(3-fluorophenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea;

N-[3-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea;

N-[3-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea;

N-[3-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea;

N-[3-(difluoromethoxy)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[3-(difluoromethoxy)phenyl]-N'-phenylurea;

N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-(3-methylphenyl)urea;

N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-(4-methylphenyl)urea;

N-[4-(4,5-dichloro-1H-imidazol-1-yl)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-ethylphenyl)urea;

N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-methylphenyl)urea;

N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2,3-dihydro-1,4-benzodioxin-6-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2,3-dihydro-1H-inden-5-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2,6-dimethylpyrimidin-4-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2-methyl-1,3-benzoxazol-6-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2-methylquinolin-6-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(2-oxo-2,3-dihydro-1-benzofuran-6-yl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethoxyphenyl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-ethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-fluorophenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-hydroxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-isopropoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-isoquinolin-4-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-methoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-oxo-2,3-dihydro-1H-inden-5-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-phenoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrazin-2-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-2-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-3-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrimidin-5-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-quinolin-3-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-quinolin-6-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-ethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-methylpyridin-2-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-phenoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-piperidin-1-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-propoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-propylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-pyrrolidin-1-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyridin-3-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyrimidin-4-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-[1-(methylsulfonyl)-2,3-dihydro-1H-indol-5-yl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-oxazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-thiazol-2-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-hydroxyethoxy)phenyl]urea;

N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-methylquinolin-6-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3-methyl-1H-pyrazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-ethylpyrazin-2-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-methoxypyridin-3-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(pyrimidin-2-yloxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-methoxy-5-(trifluoromethyl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(phenoxymethyl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(piperidin-1-ylsulfonyl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(pyrrolidin-1-ylsulfonyl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[6-(difluoromethoxy)pyrimidin-4-yl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[6-(trifluoromethyl)pyridin-3-yl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[2-methoxy-5-(trifluoromethyl)pyrimidin-4-yl]phenyl}urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl]phenyl}urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[5-(1-ethylpropoxy)-6-(methylamino)pyridin-2-yl]phenyl}urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[5-(trifluoromethyl)pyridin-2-yl]phenyl}urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[6-methoxy-3-(trifluoromethyl)pyridin-2-yl]phenyl}urea;
N-[4-(difluoromethoxy)phenyl]-N'-1H-indazol-5-ylurea;
N-[4-(difluoromethoxy)phenyl]-N'-phenylurea;
N-[4-(difluoromethoxy)phenyl]-N'-quinolin-3-ylurea;
N-[4-(difluoromethoxy)phenyl]-N'-quinolin-5-ylurea;
N-[4-(difluoromethoxy)phenyl]-N'-quinolin-6-ylurea;
N-[4-(methoxymethyl)phenyl]-N'-(4-methylphenyl)urea;
N-biphenyl-3-yl-N'-[4-(difluoromethoxy)phenyl]urea;
N-biphenyl-4-yl-N'-[4-(difluoromethoxy)phenyl]urea;
N-phenyl-N'-(4-piperidin-1-ylphenyl)urea;
N-phenyl-N'-(4-propoxyphenyl)urea; or
N-phenyl-N'-(4-propylphenyl)urea.

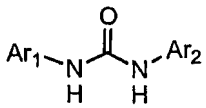
14. A method according to any one of claims 1-13, wherein the condition is an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss.

15. A method according to claim 14, wherein the condition is obesity, bulimia, alcohol dependency or nicotine dependency.

16. A method according to claim 15, wherein the condition is obesity.

17. A pharmaceutical composition, comprising:

(a) a first agent that is a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 and Ar_2 are independently chosen from phenyl and 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents independently chosen from R_x; and

Each R_x is independently:

(i) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(ii) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

M is absent, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, $S(O)_m$, $N(R_z)$, $C(=O)N(R_z)$, $C(=NH)N(R_z)$, $N(R_z)C(=O)$, $N(R_z)C(=NH)$, $N(R_z)C(=O)O$, $OC(=O)N(R_z)$, $N(R_z)S(O)_m$, $S(O)_mN(R_z)$ and $N[S(O)_mR_z]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(iii) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl;

(b) a second agent that is suitable for treating an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss; and

(c) a physiologically acceptable carrier or excipient.

18. A pharmaceutical composition according to claim 17, wherein the second agent is an anti-obesity agent selected from an MCH receptor antagonist, an apo-B/MTP inhibitor, a 11β-hydroxy steroid dehydrogenase-1 inhibitor, peptide YY_3-36 or an analog thereof, a MCR-4 agonist, a CCK-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a β_3 adrenergic receptor agonist, a dopamine agonist, a melanocyte-stimulating hormone receptor analog, a 5-HT2c receptor agonist, leptin or an analog thereof, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a neuropeptide-Y receptor antagonist, a thyromimetic agent, dehydroepiandrosterone or analog thereof, a glucocorticoid receptor antagonist, an orexin receptor antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, a human agouti-related protein antagonist, a ghrelin receptor antagonist, a histamine 3 receptor antagonist, or a neuromedin U receptor agonist.

19. A pharmaceutical composition according to claim 18, wherein the anti-obesity agent is phentermine, orlistat or sibutramine.

20. A pharmaceutical composition according to claim 17, wherein the second agent is a nicotine receptor partial agonist, an opioid antagonist or a dopaminergic agent.

21. A pharmaceutical composition according to claim 17, wherein the second agent is suitable for treating an addictive disorder, and wherein the agent is selected from methadone, LAAM, naltrexone, ondansetron, sertraline, fluoxetine, diazepam, chlordiazepoxide, varenicline and bupropion.

22. A pharmaceutical composition according to any one of claims 17-21, wherein Ar_1 and Ar_2 are independently phenyl, pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently located *meta* or *para* to the point of attachment, wherein each substituent is independently:

(a) halogen, hydroxy or cyano; or

(b) C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_4alkanoyl, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl or a 5- or 6-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, and C_1-C_4haloalkyl.

23. A pharmaceutical composition according to any one of claims 17-22, wherein Ar_1 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy.

24. A pharmaceutical composition according to claim 23, wherein Ar_1 is phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-(C_1-C_4alkyl)phenyl, 4-(C_1-C_4alkyl)phenyl, 3-(C_1-C_4alkoxy)phenyl or 4-(C_1-C_4alkoxy)phenyl.

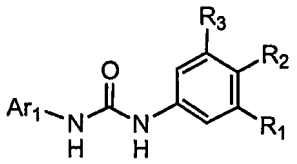
25. A pharmaceutical composition according to any one of claims 17-24, wherein Ar_2 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle.

26. A pharmaceutical composition according to claim 25, wherein Ar_2 is phenyl that is substituted with exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

27. A pharmaceutical composition according to claim 25, wherein Ar_2 is phenyl that is substituted with exactly one substituent chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

28. A pharmaceutical composition according to claim 27, wherein Ar_2 is phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-cyano-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-cyano-phenyl, 3-(C_1-C_4alkyl)phenyl, 4-(C_1-C_4alkyl)phenyl, 3-(C_1-C_4alkoxy)phenyl or 4-(C_1-C_4alkoxy)phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl or 4-acetyl-phenyl.

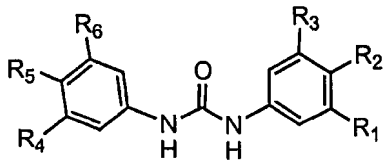
29. A pharmaceutical composition according to claim 17, wherein the compound has the formula:



wherein R_1, R_2 and R_3 are independently chosen from hydrogen and R_x, and wherein at least one of R_1 and R_2 is not hydrogen.

30. A pharmaceutical composition according to claim 29, wherein R_1, R_2 and R_3 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl and 5- and 6-membered heterocycles.

31. A pharmaceutical composition according to claim 17, wherein the compound has the formula:

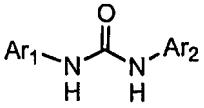


wherein R_4, R_5 and R_6 are independently chosen from hydrogen and R_x, and wherein at least one of R_4 and R_5 is not hydrogen.

32. A pharmaceutical composition according to claim 31, wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

33. A packaged pharmaceutical preparation, comprising:

(a) pharmaceutical composition comprising a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 and Ar_2 are independently chosen from phenyl and 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(i) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(ii) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

M is absent, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, $S(O)_m$, $N(R_z)$, $C(=O)N(R_z)$, $C(=NH)N(R_z)$, $N(R_z)C(=O)$, $N(R_z)C(=NH)$, $N(R_z)C(=O)O$, $OC(=O)N(R_z)$, $N(R_z)S(O)_m$, $S(O)_mN(R_z)$ and $N[S(O)_mR_z]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(iii) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl;

in combination with a physiologically acceptable carrier or excipient; and

(b) instructions for using the composition to treat an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss.

34. A packaged pharmaceutical preparation according to claim 33, wherein Ar_1 and Ar_2 are independently phenyl, pyridyl or pyrimidyl, each of which is substituted with from 0 to 3 substituents independently located *meta* or *para* to the point of attachment, wherein each substituent is independently:

(a) halogen, hydroxy or cyano; or

(b) C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_1-C_4alkanoyl, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl or a 5- or 6-membered heterocycle, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, and C_1-C_4haloalkyl.

35. A packaged pharmaceutical preparation according to claim 33 or claim 34, wherein Ar_1 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl or C_1-C_4haloalkoxy.

36. A packaged pharmaceutical preparation according to claim 32, wherein Ar_1 is phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl or 4-(C_1-C_4alkoxy)-phenyl.

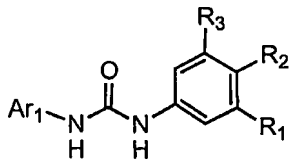
37. A packaged pharmaceutical preparation according to any one of claims 33-36, wherein Ar_2 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle.

38. A packaged pharmaceutical preparation according to claim 37, wherein Ar_2 is phenyl that is substituted with exactly two substituents independently chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

39. A packaged pharmaceutical preparation according to claim 37, wherein Ar_2 is phenyl that is substituted with exactly one substituent chosen from halogen, C_1-C_2alkyl, C_1-C_2alkoxy and C_1-C_2haloalkoxy.

40. A packaged pharmaceutical preparation according to claim 39, wherein Ar_2 is phenyl, 3-halo-phenyl, 4-halo-phenyl, 3-cyano-phenyl, 3-hydroxy-phenyl, 4-hydroxy-phenyl, 4-cyano-phenyl, 3-(C_1-C_4alkyl)-phenyl, 4-(C_1-C_4alkyl)-phenyl, 3-(C_1-C_4alkoxy)-phenyl or 4-(C_1-C_4alkoxy)-phenyl, 3-difluoromethoxy-phenyl, 4-difluoromethoxy-phenyl, 3-acetyl-phenyl or 4-acetyl-phenyl.

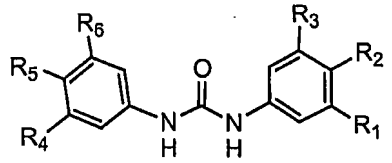
41. A packaged pharmaceutical preparation according to claim 33, wherein the compound has the formula:



wherein R_1, R_2 and R_3 are independently chosen from hydrogen and R_x, and wherein at least one of R_1 and R_2 is not hydrogen.

42. A packaged pharmaceutical preparation according to claim 41, wherein R_1, R_2 and R_3 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl and 5- and 6-membered heterocycles.

43. A packaged pharmaceutical preparation according to claim 41, wherein the compound has the formula:

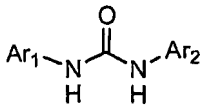


wherein R_4, R_5 and R_6 are independently chosen from hydrogen and R_x, and wherein at least one of R_4 and R_5 is not hydrogen.

44. A packaged pharmaceutical preparation according to claim 43, wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl, phenyl and 5- and 6-membered heterocycles.

45. A method for identifying a non-competitive CB1 antagonist, comprising:

(a) contacting CB1 with a labeled, non-competitive CB1 antagonist and a test compound, under conditions that permit binding of the CB1 antagonist to CB1; wherein the CB1 antagonist is a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 and Ar_2 are independently chosen from phenyl and 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(i) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(ii) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

M is absent, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, $S(O)_m$, $N(R_z)$, $C(=O)N(R_z)$, $C(=NH)N(R_z)$, $N(R_z)C(=O)$, $N(R_z)C(=NH)$, $N(R_z)C(=O)O$, $OC(=O)N(R_z)$, $N(R_z)S(O)_m$, $S(O)_mN(R_z)$ and $N[S(O)_mR_z]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(iii) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl;

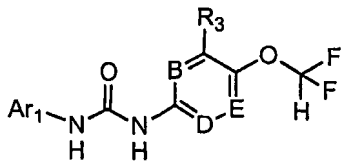
(b) removing unbound labeled, non-competitive CB1 antagonist and test compound;

(c) detecting a signal that corresponds to the amount of labeled, non-competitive CB1 antagonist bound to the CB1; and

(d) comparing the signal to a reference signal that corresponds to the amount of labeled, non-competitive CB1 antagonist bound to the CB1 in the absence of test compound;

and therefrom identifying a non-competitive CB1 antagonist.

46. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

B, D and E are independently CH or N;

R_3 is hydrogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; such that if R_3 is hydrogen, then Ar_1 is substituted with at least one substituent that is not a halogen; and

Each R_x is independently:

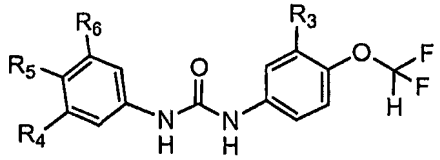
(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, amino, cyano, C_1-C_4alkyl and C_1-C_4alkoxy.

47. A compound or salt according to claim 46, wherein R_3 is hydrogen, methoxy or difluoromethoxy.

48. A compound or salt according to claim 46 or claim 47, wherein Ar_1 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle.

49. A compound or salt according to any one of claims 46-48, wherein the compound has the formula:



wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

50. A compound or salt according to claim 46, wherein the compound is:

ethyl 3-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]benzoate;

methyl 4-[({[4-(difluoromethoxy)phenyl]amino}carbonyl)amino]-2-methoxybenzoate;

N-(2-amino-5-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(3-cyclopropyl-1H-pyrazol-5-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(4-acetylphenyl)-N'-[4-(difluoromethoxy)phenyl]urea;
N-(6-bromopyridin-3-yl)-N'-[4-(difluoromethoxy)phenyl]urea;
N,N'-bis[4-(difluoromethoxy)-3-methoxyphenyl]urea;
N,N'-bis[4-(difluoromethoxy)phenyl]urea;
N-[3-(2-hydroxyethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[3-(difluoromethoxy)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-ethylphenyl)urea;
N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-(4-methylphenyl)urea;
N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(difluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)-3-methoxyphenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-(2,6-dimethylpyrimidin-4-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,4-dimethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3,5-dimethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-ethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-hydroxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-isopropoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-methoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-phenyl-1H-pyrazol-5-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrazin-2-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-2-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyridin-3-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(3-pyrimidin-5-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-ethoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-methylpyridin-2-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-piperidin-1-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-propoxyphenyl)urea;

N-[4-(difluoromethoxy)phenyl]-N'-(4-propylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(4-pyrrolidin-1-ylphenyl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyridin-3-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-(6-methoxypyrimidin-4-yl)urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-oxazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(1,3-thiazol-2-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-hydroxyethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(2-methylpyrimidin-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(3-methyl-1H-pyrazol-4-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-ethylpyrazin-2-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(6-methoxypyridin-3-yl)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[4-(trifluoromethoxy)phenyl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-[6-(difluoromethoxy)pyrimidin-4-yl]urea;
N-[4-(difluoromethoxy)phenyl]-N'-{3-[5-(trifluoromethyl)pyridin-2-yl]phenyl}urea;
N-biphenyl-3-yl-N'-[4-(difluoromethoxy)phenyl]urea; or
N-biphenyl-4-yl-N'-[4-(difluoromethoxy)phenyl]urea.

51. A pharmaceutical composition, comprising a compound according to claim 46 in combination with a physiologically acceptable carrier or excipient.

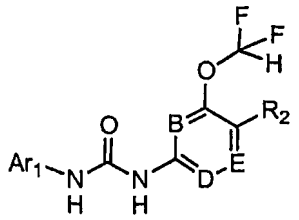
52. A method for treating a condition responsive to CB1 modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 46.

53. A method according to claim 52, wherein the condition is an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss.

54. A method according to claim 53, wherein the condition is obesity, bulimia, alcohol dependency or nicotine dependency.

55. A method according to claim 54, wherein the condition is obesity.

56. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

B, D and E are independently CH or N;

R_2 is hydrogen, halogen, cyano, C_1-C_4alkoxy or C_1-C_4haloalkoxy;

Ar_1 is phenyl or a 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

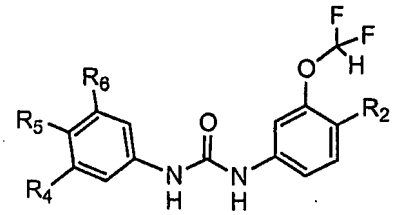
(a) hydroxy, halogen, amino, nitro, aminocarbonyl, aminosulfonyl or –COOH; or

(b) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6alkanone, C_1-C_6alkanoyl, C_1-C_6alkoxycarbonyl, C_2-C_6alkanoyloxy, C_1-C_6alkylthio, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, C_1-C_6alkylsulfonyl, phenyl or 5- or 6-membered heterocycle; each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, amino and cyano.

57. A compound or salt according to claim 56, wherein R_2 is hydrogen, halogen, methoxy or difluoromethoxy.

58. A compound or salt according to claim 56 or claim 57, wherein Ar_1 is phenyl that is unsubstituted or substituted with 1 or 2 substituents, each of which is located *meta* or *para* to the point of attachment, and each of which is independently halogen, hydroxy, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyl or a 5- or 6-membered heterocycle.

59. A compound or salt according to any one of claims 56-57, wherein the compound has the formula:



wherein R_4, R_5 and R_6 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_2-C_4alkanoyloxy, C_1-C_4alkoxycarbonyl and 5- and 6-membered heterocycles.

60. A compound or salt according to claim 56, wherein the compound is:
N-[3-(difluoromethoxy)phenyl]-N'-[4-(difluoromethoxy)phenyl]urea;

N,N'-bis[3-(difluoromethoxy)phenyl]urea;
N-(3-chloro-4-morpholin-4-ylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-[3-(difluoromethoxy)phenyl]-N'-(4-isopropoxyphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-[3-(trifluoromethoxy)phenyl]urea;
N-[3-(difluoromethoxy)phenyl]-N'-[3-(3,5-dimethylisoxazol-4-yl)phenyl]urea;
N-[3-(difluoromethoxy)phenyl]-N'-[3-(2,6-dimethylpyridin-4-yl)phenyl]urea;
N-[3-(difluoromethoxy)phenyl]-N'-(3-methylphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(4-methylphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(3-fluorophenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(4-fluorophenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-phenylurea;
N-[3-(difluoromethoxy)phenyl]-N'-(2-methylphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(2-ethylphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(3-ethylphenyl)urea;
N-[3-(difluoromethoxy)phenyl]-N'-(4-ethylphenyl)urea;
N-(3-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(4-chlorophenyl)-N'-[3-(difluoromethoxy)phenyl]urea;
N-(3-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea; or
N-(4-acetylphenyl)-N'-[3-(difluoromethoxy)phenyl]urea.

61. A pharmaceutical composition, comprising a compound according to claim 56 in combination with a physiologically acceptable carrier or excipient.

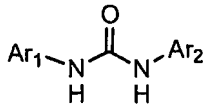
62. A method for treating a condition responsive to CB1 modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound according to claim 56.

63. A method according to claim 62, wherein the condition is an appetite disorder, obesity, an addictive disorder, asthma, liver cirrhosis, sepsis, irritable bowel disease, Crohn's disease, depression, schizophrenia, a memory disorder, a cognitive disorder, a movement disorder or bone loss.

64. A method according to claim 63, wherein the condition is obesity, bulimia, alcohol dependency or nicotine dependency.

65. A method according to claim 64, wherein the condition is obesity.

66. A method for suppressing appetite in a patient, comprising administering to the patient an appetite reducing amount of at least one compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 and Ar_2 are independently chosen from phenyl and 5- or 6-membered heteroaryl, each of which is substituted with from 0 to 4 substituents that are independently chosen from R_x; and

Each R_x is independently:

(a) hydroxy, halogen, amino, cyano, nitro, aminocarbonyl, aminosulfonyl or –COOH;

(b) a group of the formula L-M-Q, wherein:

L is absent or C_0-C_4alkylene;

M is absent, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, $S(O)_m$, $N(R_z)$, $C(=O)N(R_z)$, $C(=NH)N(R_z)$, $N(R_z)C(=O)$, $N(R_z)C(=NH)$, $N(R_z)C(=O)O$, $OC(=O)N(R_z)$, $N(R_z)S(O)_m$, $S(O)_mN(R_z)$ and $N[S(O)_mR_z]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_z is independently selected at each occurrence from hydrogen, C_1-C_8alkyl and groups that are taken together with Q to form an optionally substituted 4- to 7-membered heterocycle; and

Q is C_1-C_8alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, phenylC_0-C_4alkyl, (5- to 10-membered heterocycle)C_0-C_4alkyl or taken together with M to form a 4- to 7-membered heterocycle, each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy and C_1-C_4haloalkyl; or

(c) taken together with an R_x located on an adjacent ring carbon atom to form a fused 5- to 7-membered carbocycle or heterocycle that is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, oxo, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4haloalkyl and C_1-C_4alkylsulfonyl.

67. A method according to claim 66, wherein the compound is a compound according to claim 46 or claim 56.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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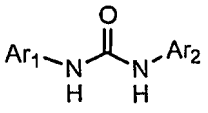

(I)

(57) Abstract: Compounds of Formula I are provided. In which the variables are as described herein. Such compounds may be used to modulate CB1 activity in vivo or in vitro, and are particularly useful in the treatment of conditions responsive to CB1 modulation in humans, domesticated companion animals and livestock animals, including appetite disorders, obesity and addictive disorders. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies and various in vitro assays.

WO 2006/049941 A3

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A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 31/196(2006.01);C07C 323/52(2006.01);C07D 271/08(2006.01)

USPC: 544/321,371;548/364;546/275.4;514/364,357
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN DATABASE SEARCH, REGISTRY, CAPLUS, MARPAT, TEXT SEARCH, MEDLINE, CAOLD, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037778 A (JANSSEN PHARMACEUTICA, N.V.) 06 May 2004, see the entire document especially abstract, compound of formula (I) on page 3, examples and claims.	1-67
A	US 5,935,978 A (FENTON et al.) 10 August 1999, see the entire document.	1-67
A	US 5,962,455 A (BLUM et al.) 05 October 1999, see the entire document.	1-67

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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